

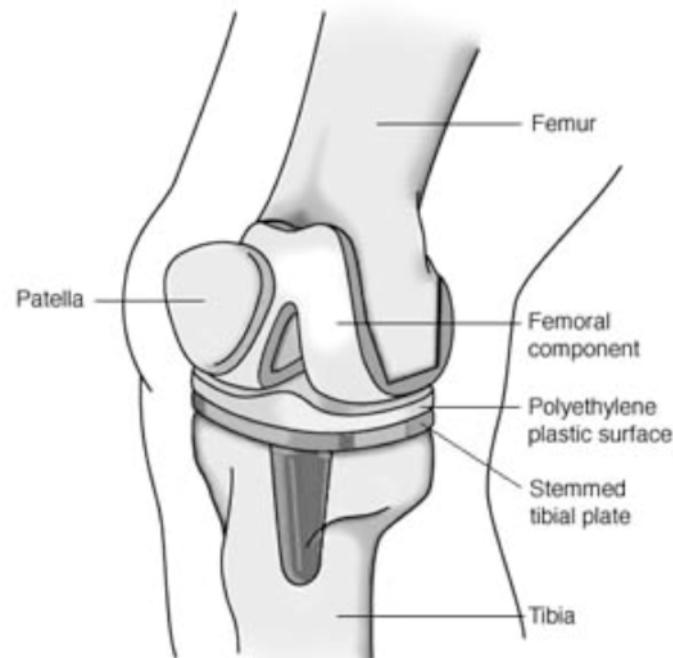
# ***Bacterial Interactions with Medical-Device Materials***

Matthew Libera  
Stevens Institute of Technology

# Overview

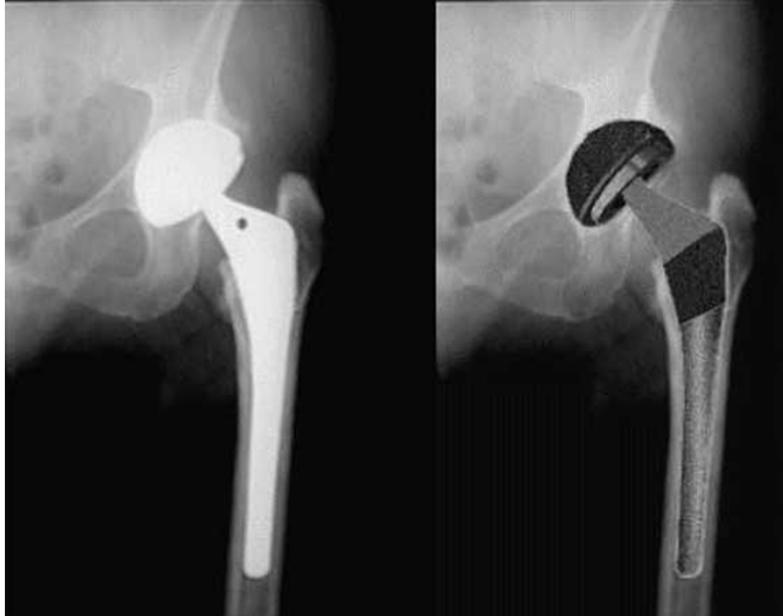
- Infection is now a leading cause of failure in many biomedical devices.
- Surface modifications to control bacterial colonization
  - Examples:
    - topography/patterning
    - antifouling surfaces
    - antibiotics (elution; tethering; triggered release)
- The next paradigm for biomaterials design and development will include infection control.

# Implanted Biomedical Devices



Total knee  
replacement

# Tissue-Integrating Biomedical Devices



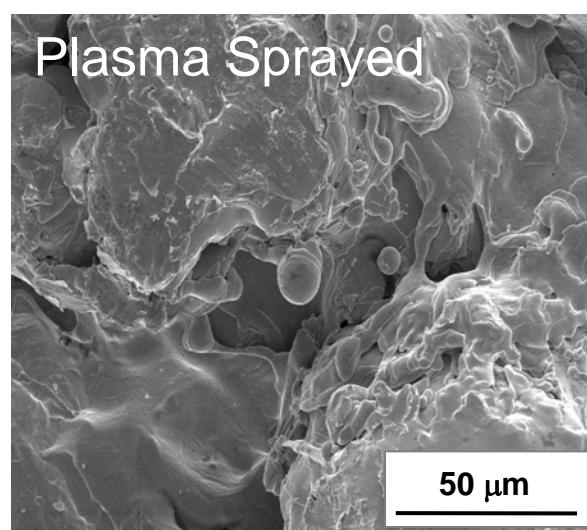
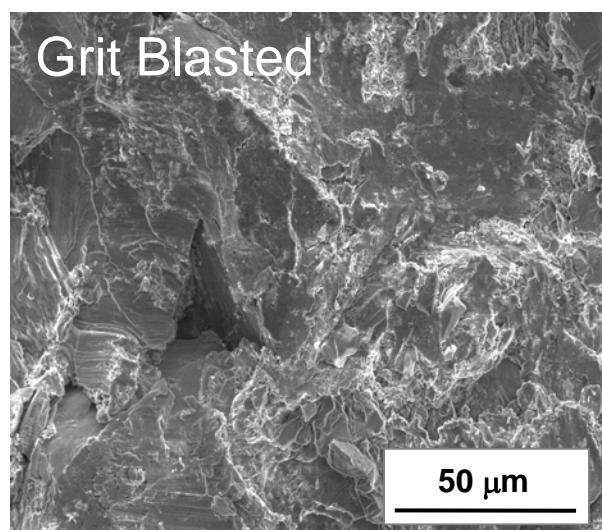
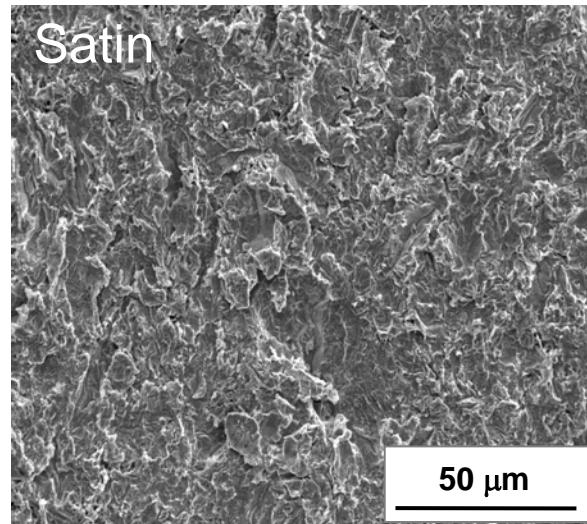
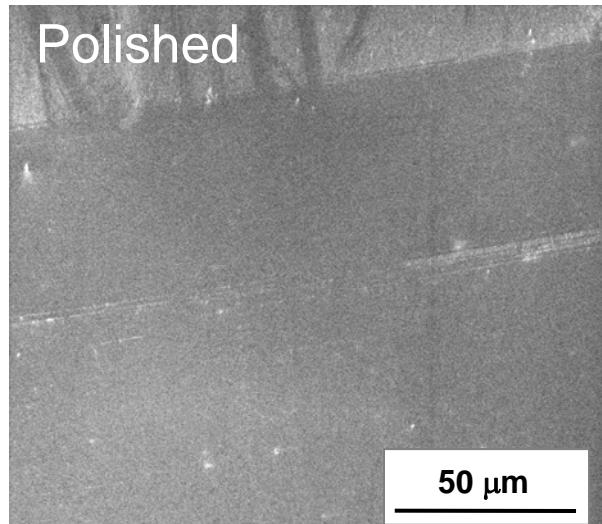
<http://healthpages.org/surgical-care/hip-joint-replacement-surgery/>

***Engineered roughness  
to control load transfer***

***Wulff's Law (~1890):  
bone adapts to load (or lack of load)***

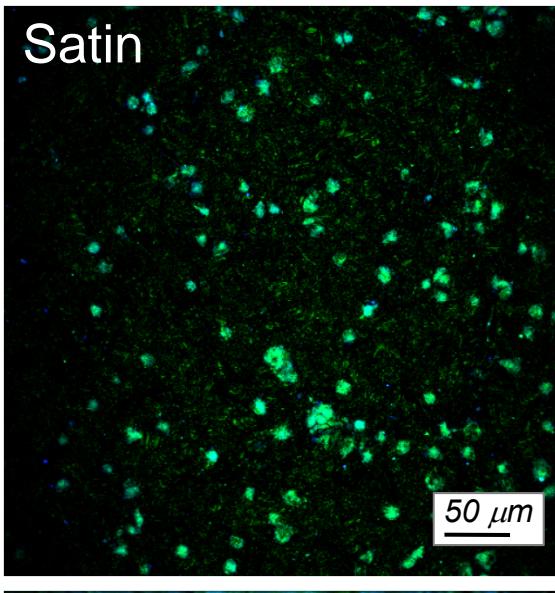


# Various Levels of Implant Surface Roughness

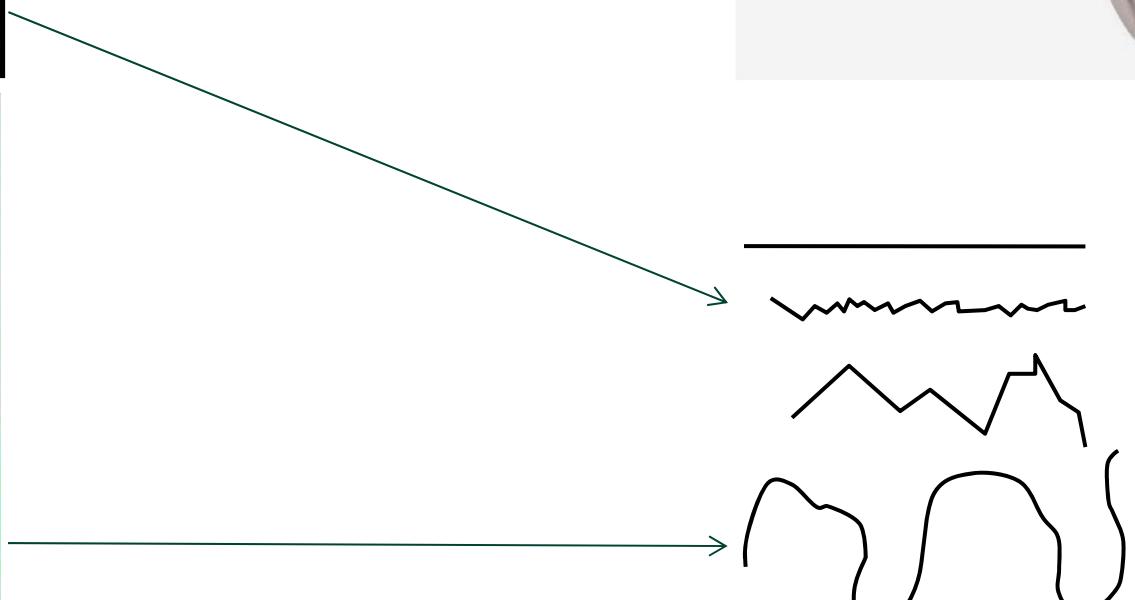
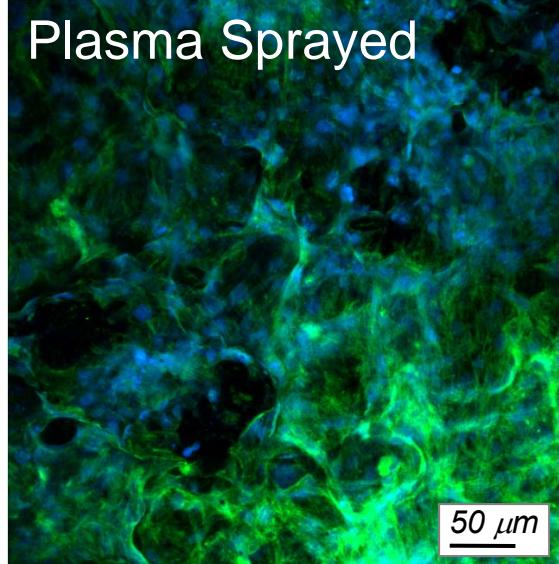


Roughness variations  
both vertically and laterally





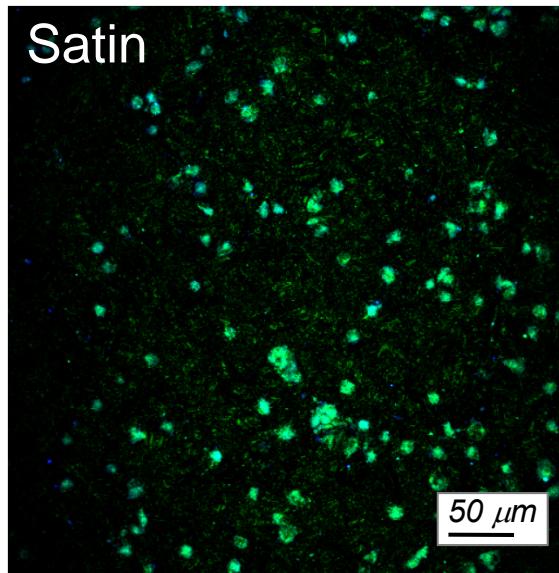
Osteoblast Adhesion and Spreading Depends on Surface Roughness



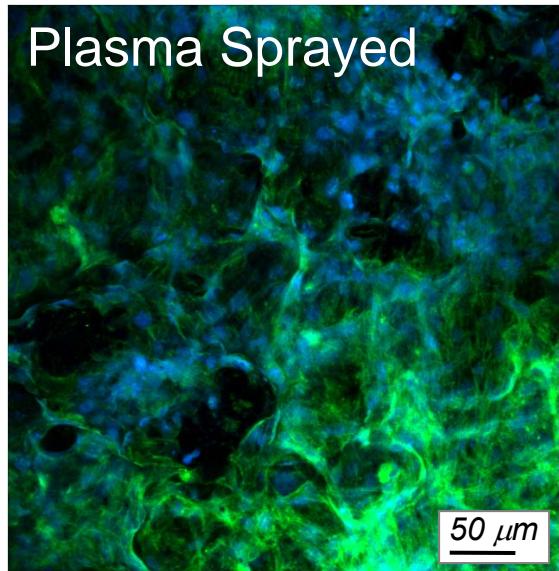
Y. Wu, J. Zitelli, K. TenHuisen, X. Yu, and M. Libera  
(2011) Biomaterials, 32 (4), pp. 951-960.

Osteoblast Adhesion/Spreading

Satin



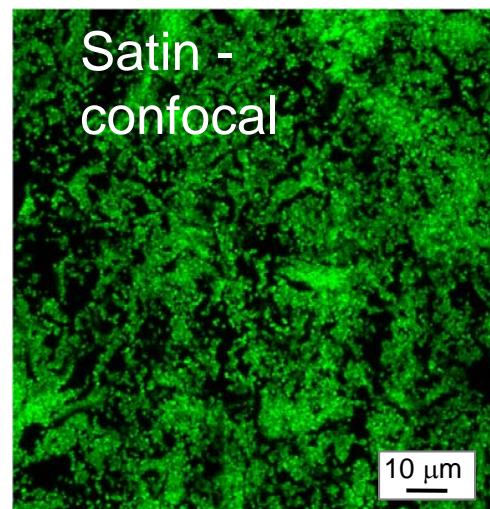
Plasma Sprayed



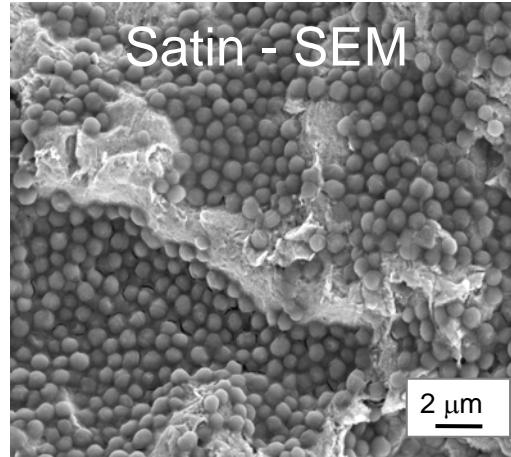
## Bacteria Like Satin-Finished Osteoblast-Resistant Surfaces

*S. epidermidis* efficiently colonizes satin finish surface

Satin -  
confocal



Satin - SEM



Y. Wu, J. Zitelli, K. TenHuisen, X. Yu, and M. Libera  
(2011) Biomaterials, 32 (4), pp. 951-960.

# Hardware-Associated Infection

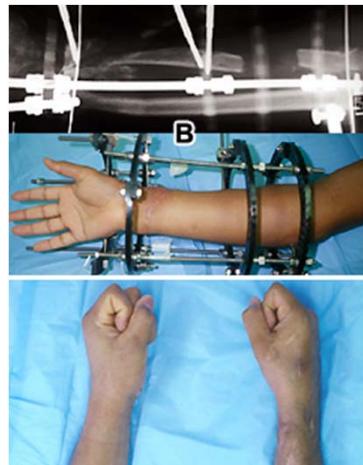
## Spinal Hardware

- Discectomy – 0.5% to 5%
- Discectomy and fusion – 5% - 8%
- Fusion without implants – 1% to 5%
- Fusion with implants – 1% to 13%



Courtesy of  
Dr. Ahmad Nassr  
Mayo Clinic

## External Fixation



Courtesy of UMDNJ

## Intramedullary Attachment for Above-the-Knee Prostheses



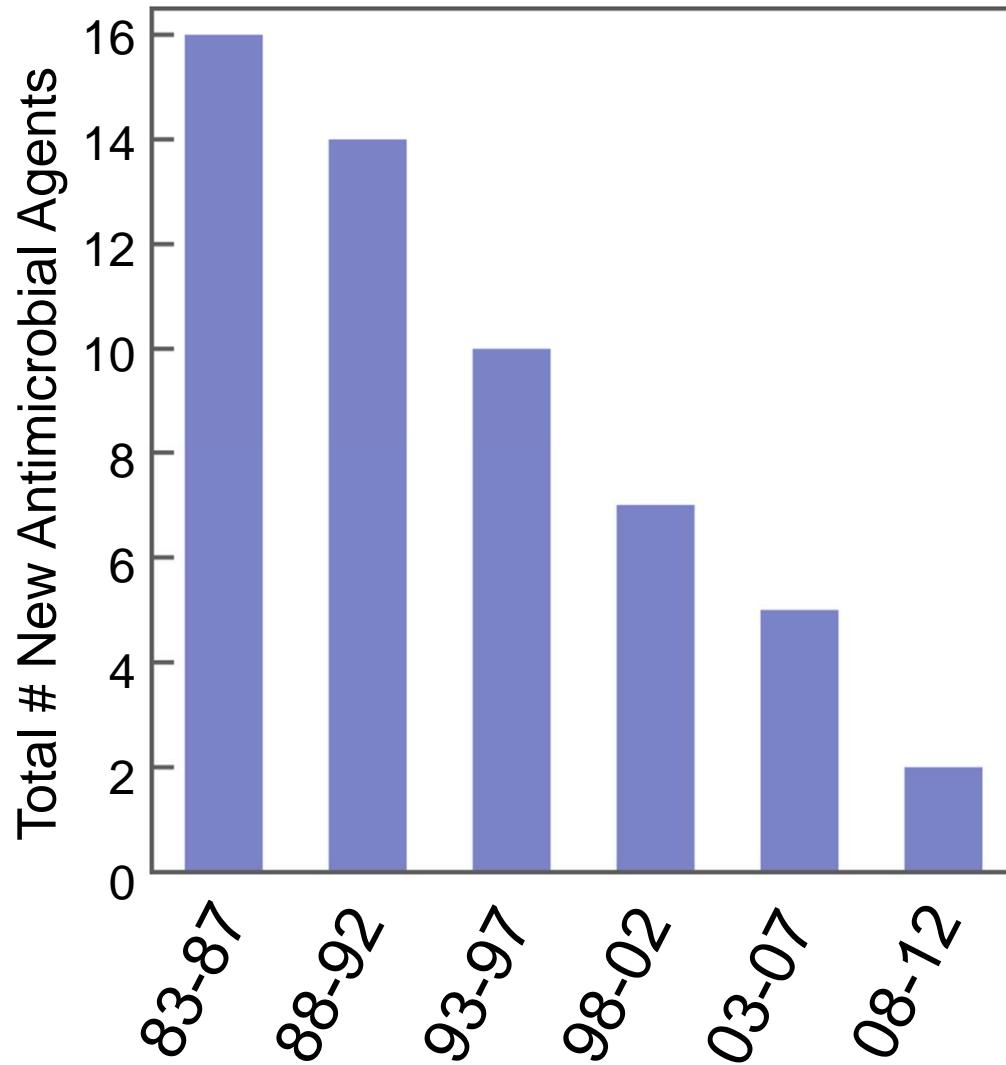
*J Bone Joint  
Surg Am.*  
2010;92  
(Sup. 2):  
180-186

## Battlefield/Civilian Trauma



“The primary risk in the use of an external fixator is infection...”

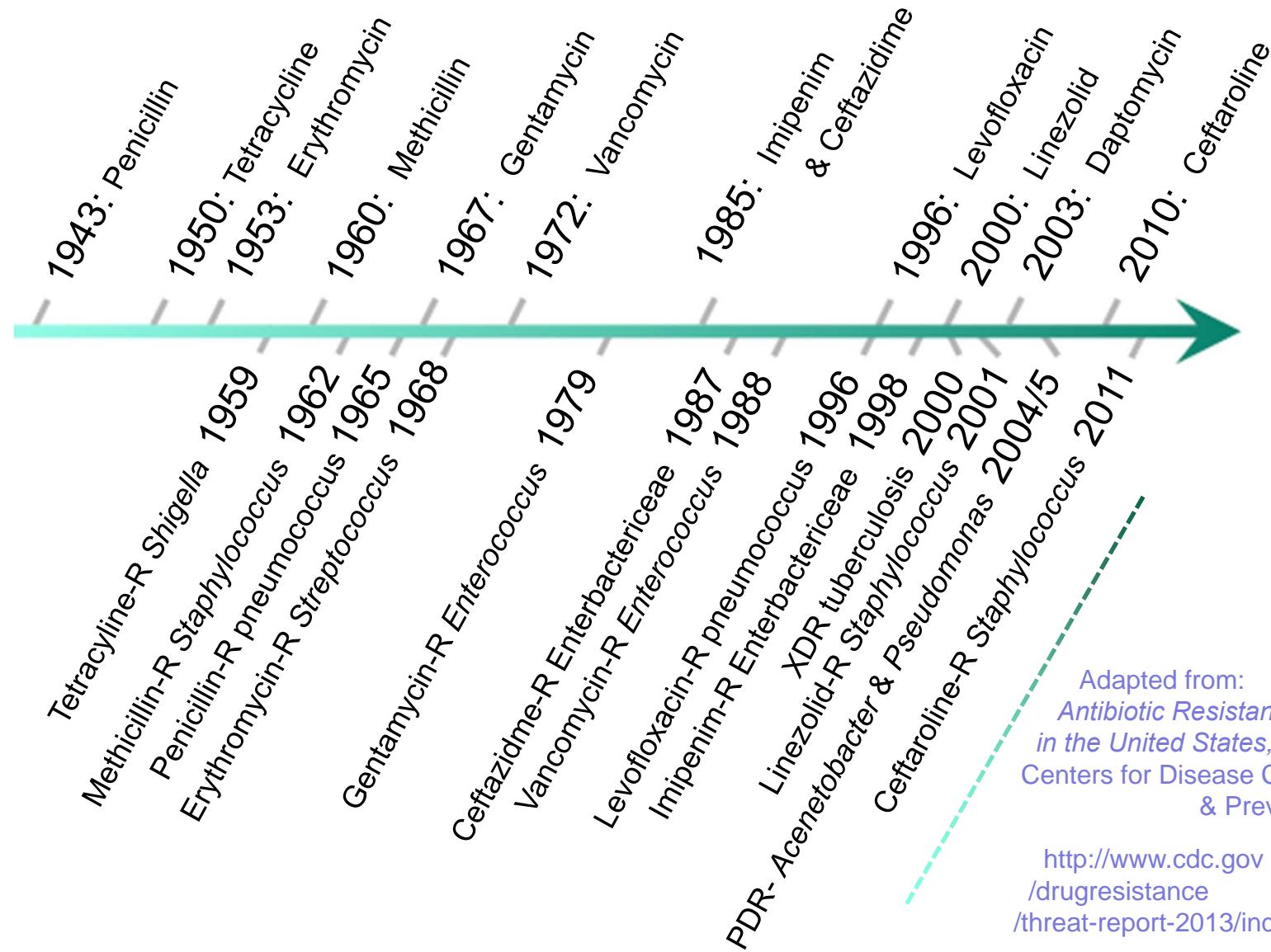
# The Number of New Antimicrobials is Declining



*Number of New and Approved Molecular Entity (NME) Systemic Antibiotics Per Five-year Period, Through 3/11.*

*Infectious Diseases Society of America (IDSA)*  
*Clin Infect Dis. 2011;52:S397-S428*

# Antibiotic resistance identified

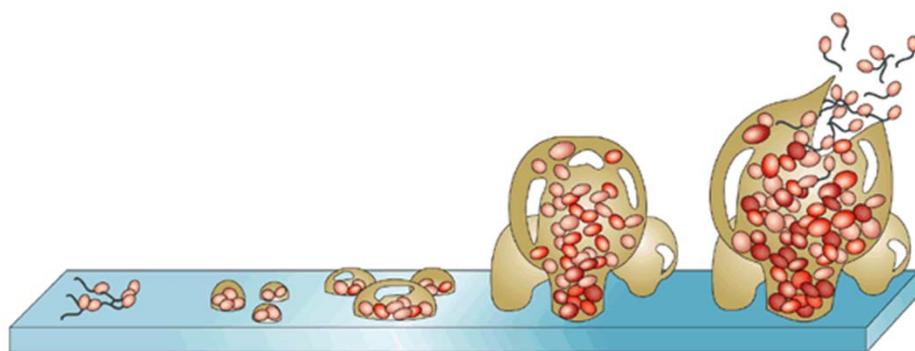


Adapted from:  
Antibiotic Resistance Threats  
in the United States, 2013.  
Centers for Disease Control  
& Prevention

[http://www.cdc.gov/  
drugresistance/  
threat-report-2013/index.html](http://www.cdc.gov/drugresistance/threat-report-2013/index.html)

# Bacterial Biofilms

- \* Bacteria colonize surfaces and develop into biofilms
- \* Bacteria in the biofilm state can be as much as 10,000 times resistant to antibiotics than planktonic bacteria



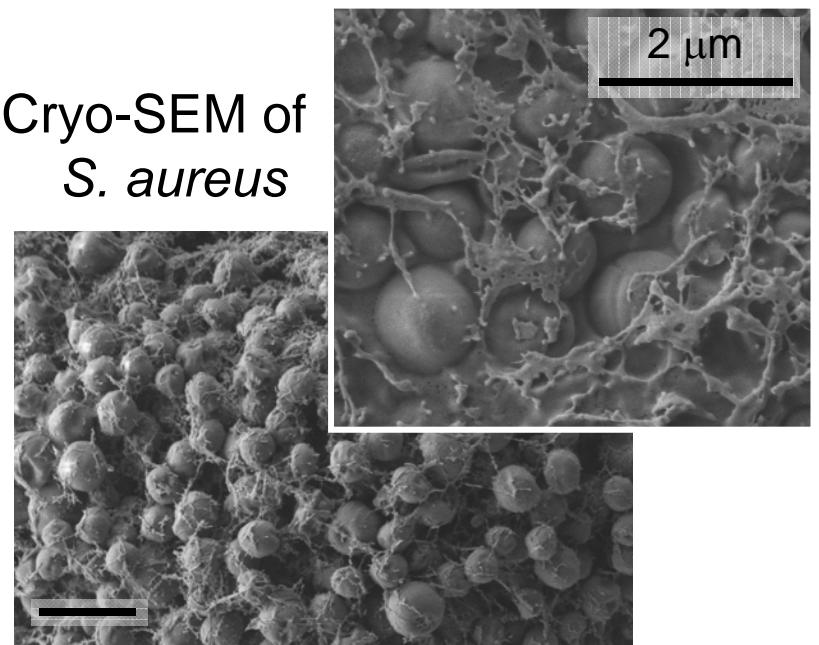
Five stages of biofilm development.

From "Understanding biofilm resistance to antibacterial agents"

David Davies

Nature Reviews Drug Discovery 2, 114-122 (February 2003)

Cryo-SEM of  
*S. aureus*



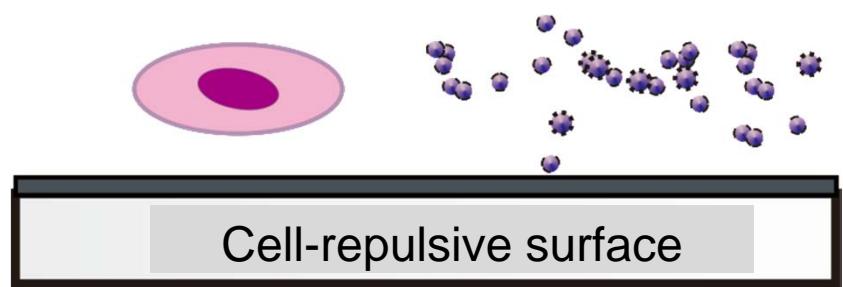
Wu et al. submitted to Microscopy and Microanalysis (2014).

# Cell/Bacteria - Material Interactions



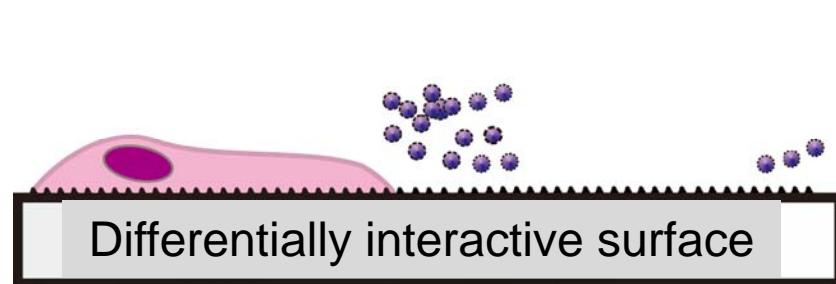
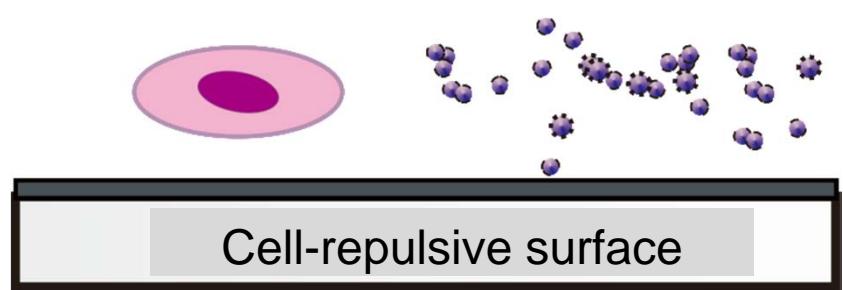
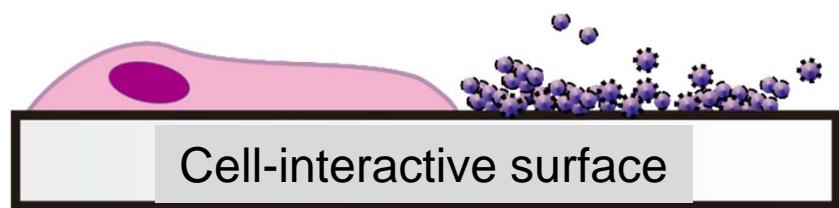
**Promotes healing  
Susceptible to infection**

# Cell/Bacteria - Material Interactions



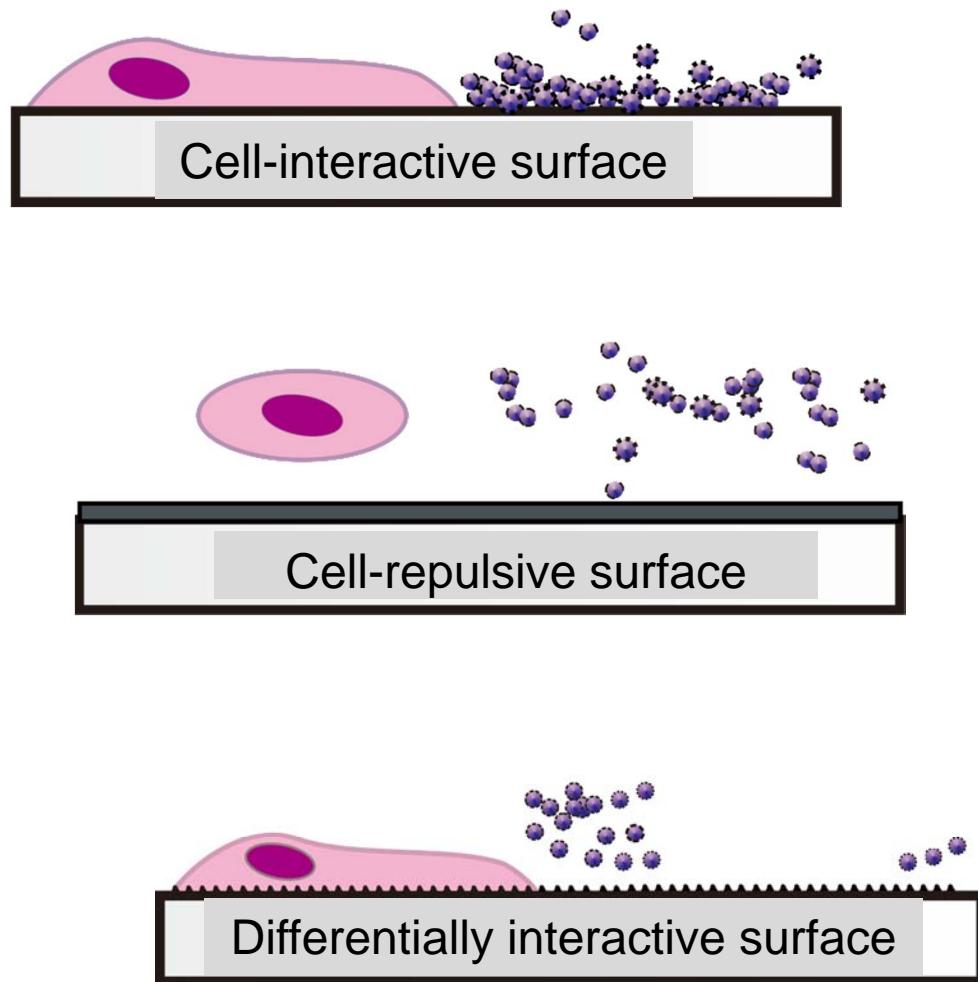
**Resists bacteria  
Can inhibit healing**

# Cell/Bacteria - Material Interactions



**Promotes healing  
Resists bacteria**

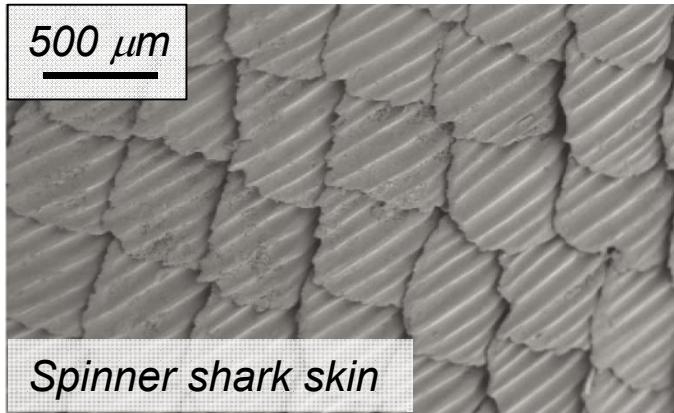
# Cell/Bacteria - Material Interactions



## Surface modifications to control bacterial colonization

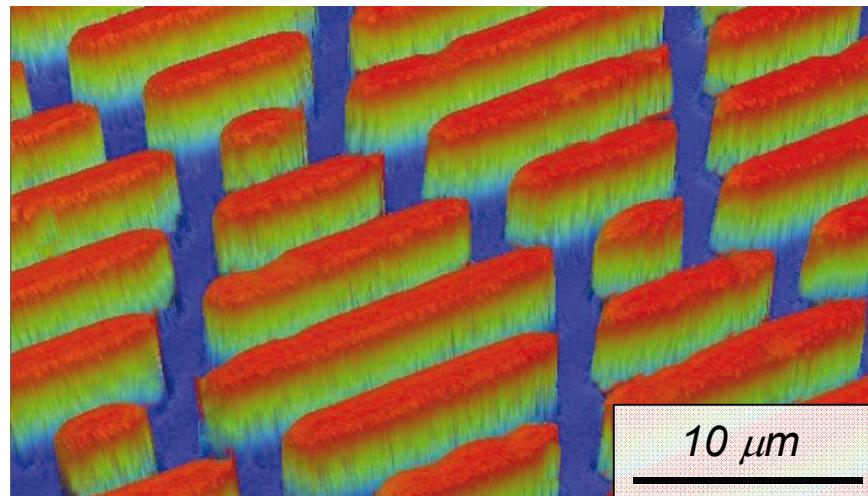
- Topography
- Patterning
- Antimicrobials
- Self-assembly  
LbL thin films  
microgel coatings

# Bio-inspired Surface Topography



Courtesy of A. Brennan  
Univ. Florida

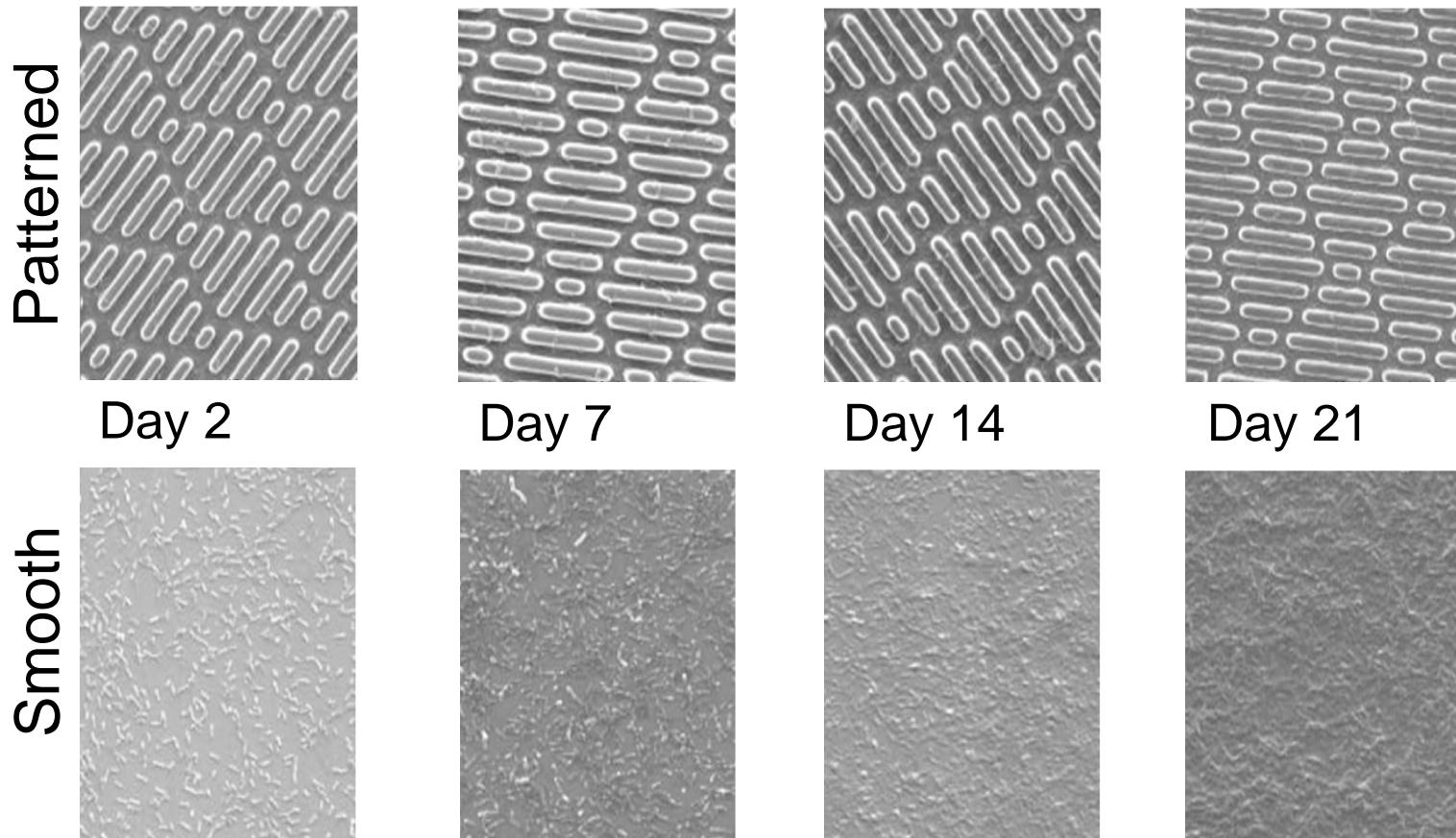
Optical profilometry of embossed PDMS surface  
2 μm width, 2 μm spacing, 3 μm depth



*Brennan et al.*  
Annual Rev. Mater. Res. 42:211-29 (2013)  
Materials Today 13: 36-44 (2010)

# Surface Topography Inhibits Bacterial Colonization

*P. aeruginosa* clinical isolate in BSA-modified TSB

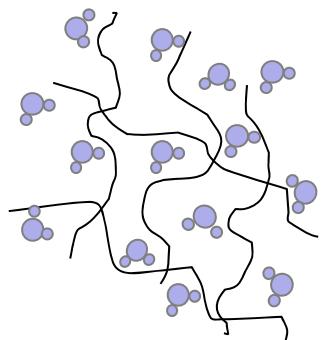


Courtesy of A. Brennan  
Univ. Florida

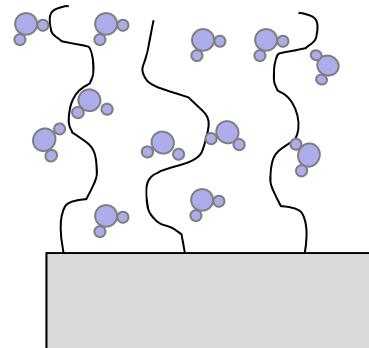
Brennan et al.  
Annual Rev. Mater. Res. 42:211-29 (2013)  
Materials Today 13: 36-44 (2010)

10  $\mu$ m

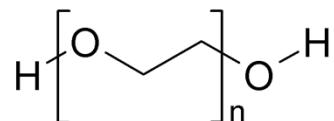
# “Antifouling” Coatings



PEG gel

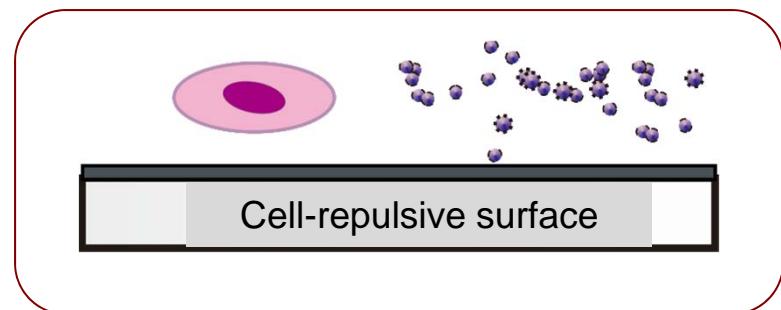


PEG monolayer  
e.g. oligo-EG thiol, silane



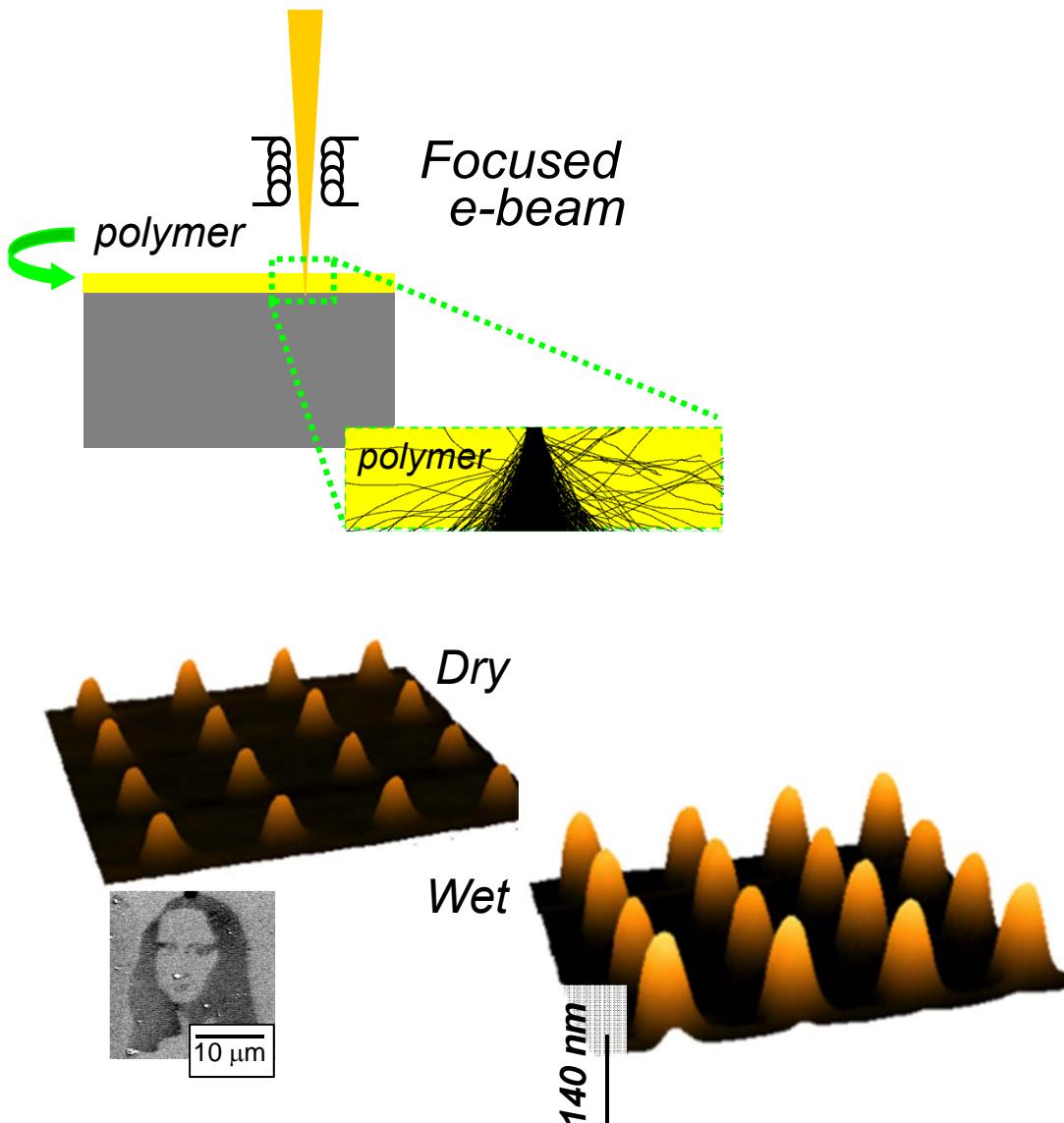
Poly(ethylene glycol) [PEG]

Jeon, Andrade, de Gennes, et al.  
*J Coll Int Sci* 142: 149 (1991)  
Prime & Whitesides  
*JACS* 115: 10714-10721 (1993)

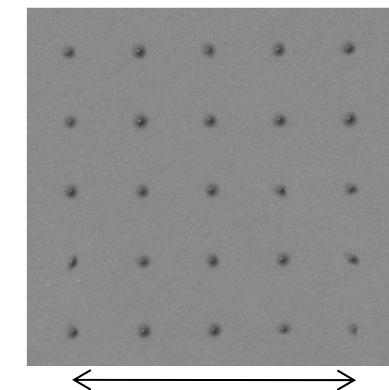
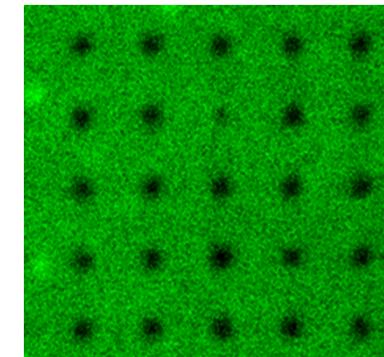


# Surface-Patterned PEG Microgels

## Laterally modulated cell adhesiveness

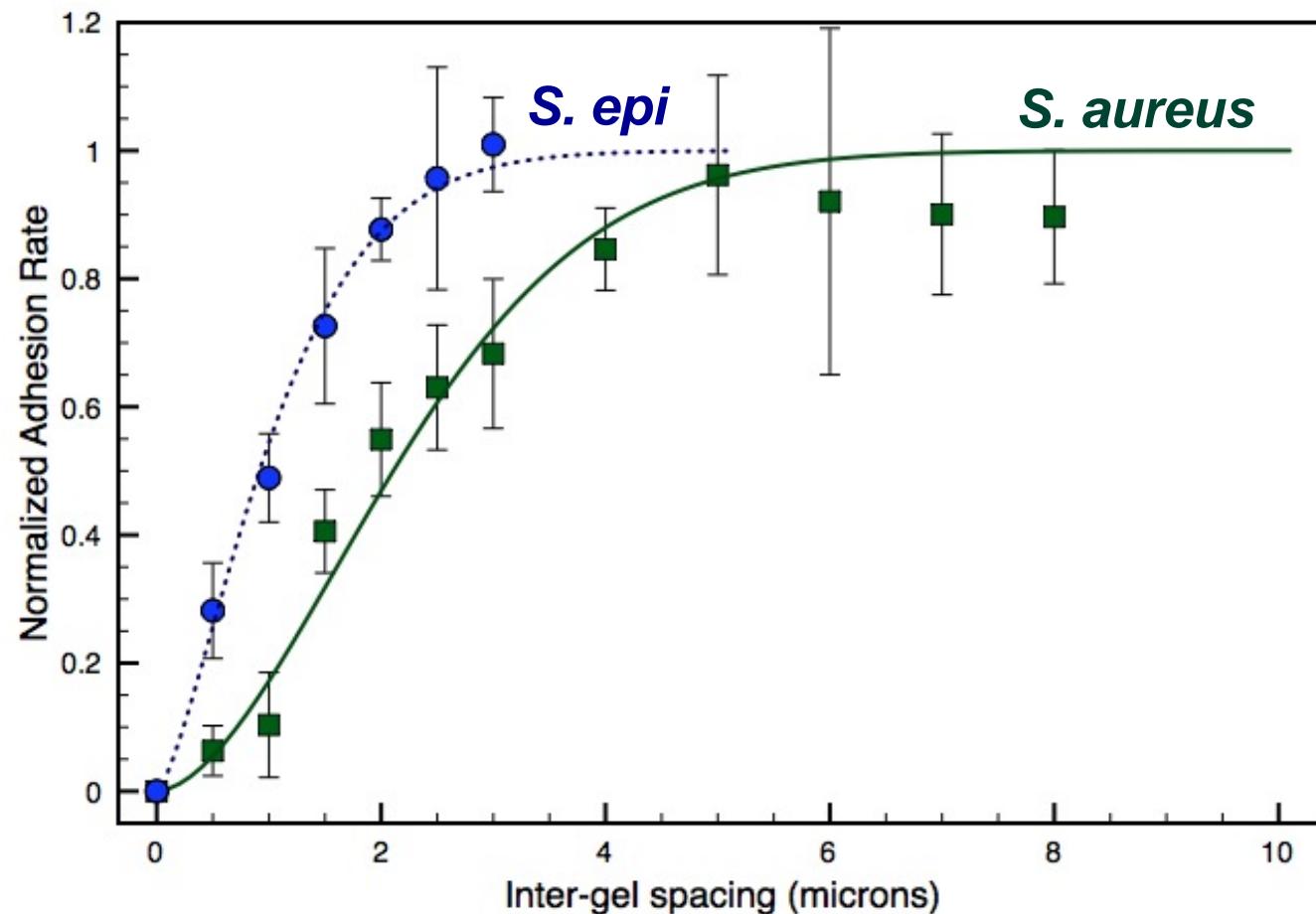


Immunofluorescence imaging of adsorbed Fibronectin (FITC) on PEG microgel patterned surface

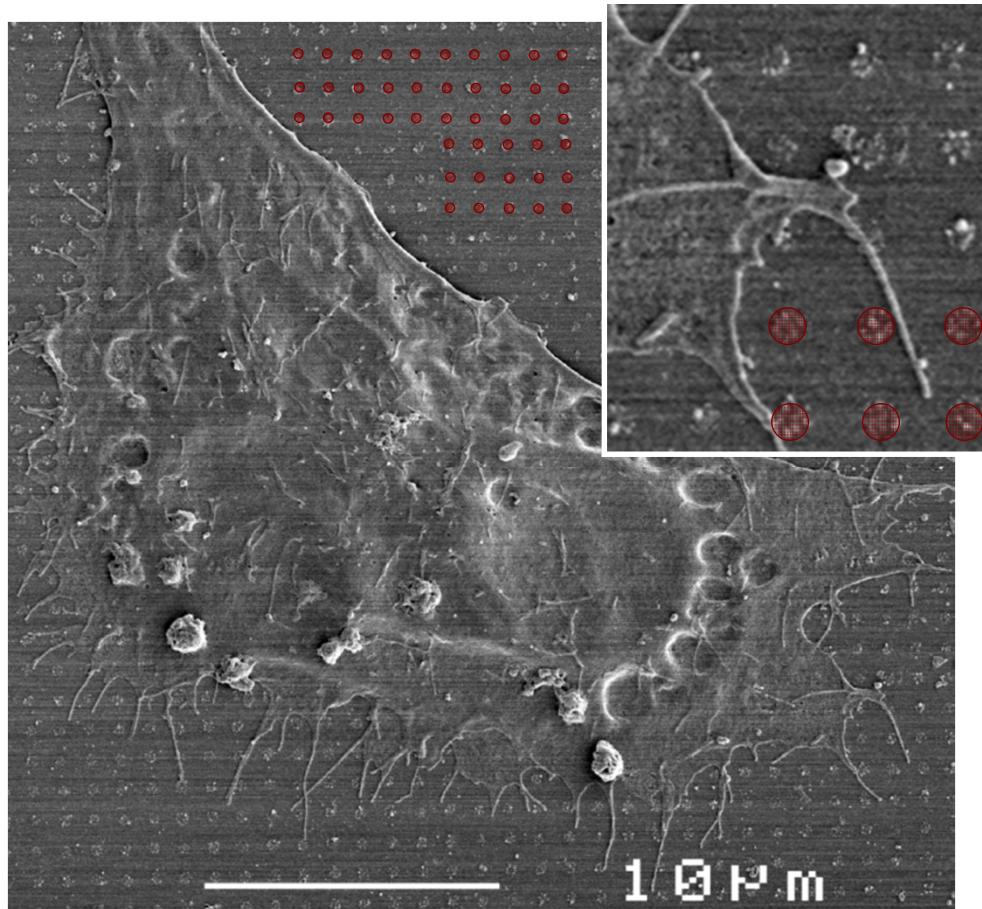


Wang et al., *Biofouling* 28 (9) (2012) 1023-1032

# The Staphylococcal Adhesion Rate Decreases with Inter-Gel Spacing ( $\delta$ )



# Osteoblasts Adhere to and Spread on Microgel-Modulated Surfaces

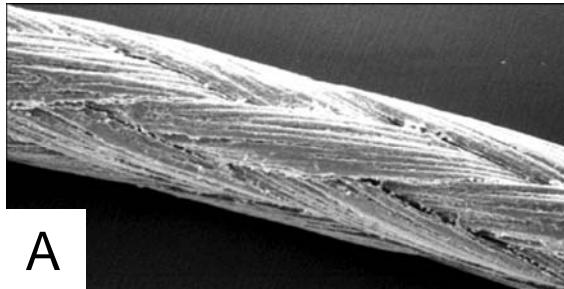


Exploits differences in:

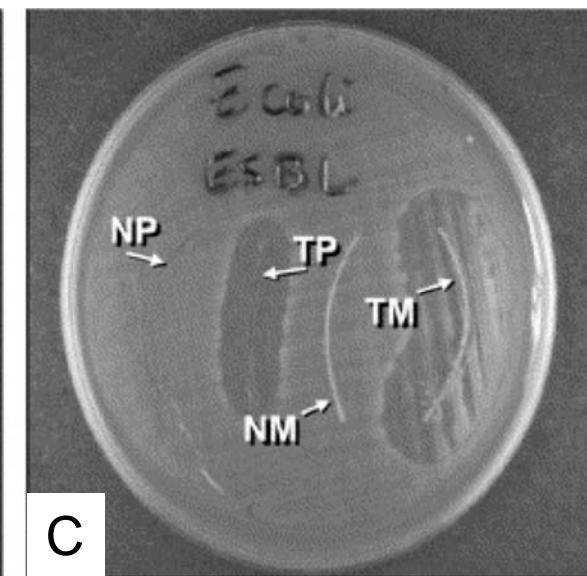
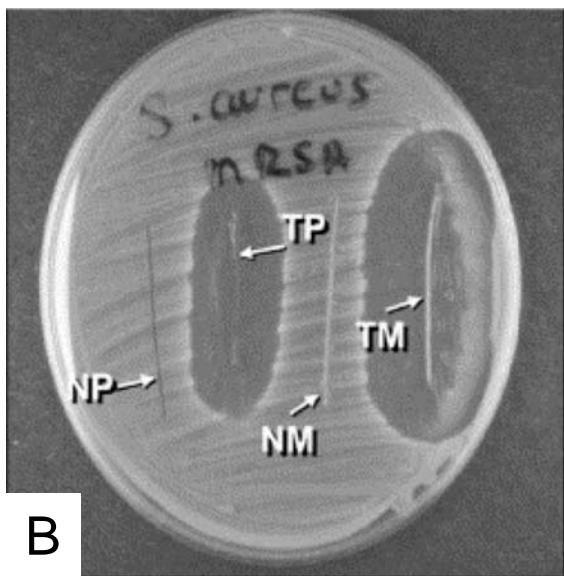
- Size
- Cell membrane/wall
- Adhesion mechanisms

Wang, Busscher et al, Advanced Functional Materials (2011)

# Active Bacterial Killing: Drug-Eluting Devices/Surfaces



TP: triclosan-coated  
polyglactin 910 suture  
TM: triclosan-impregnated  
monofilament



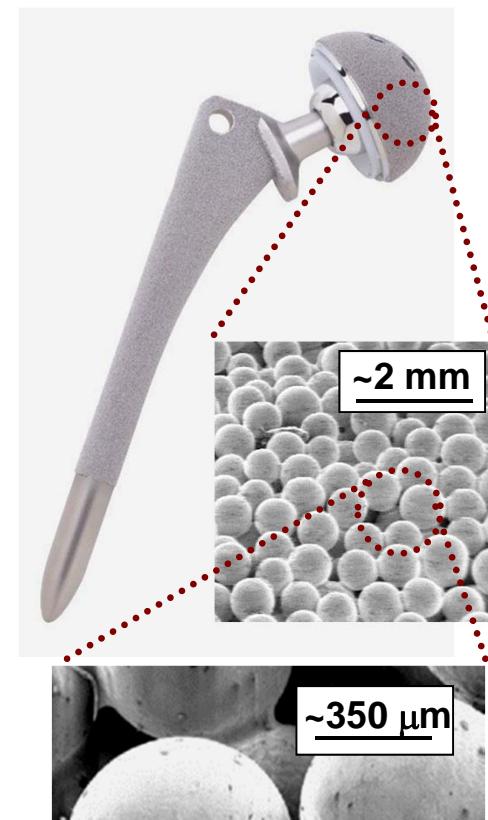
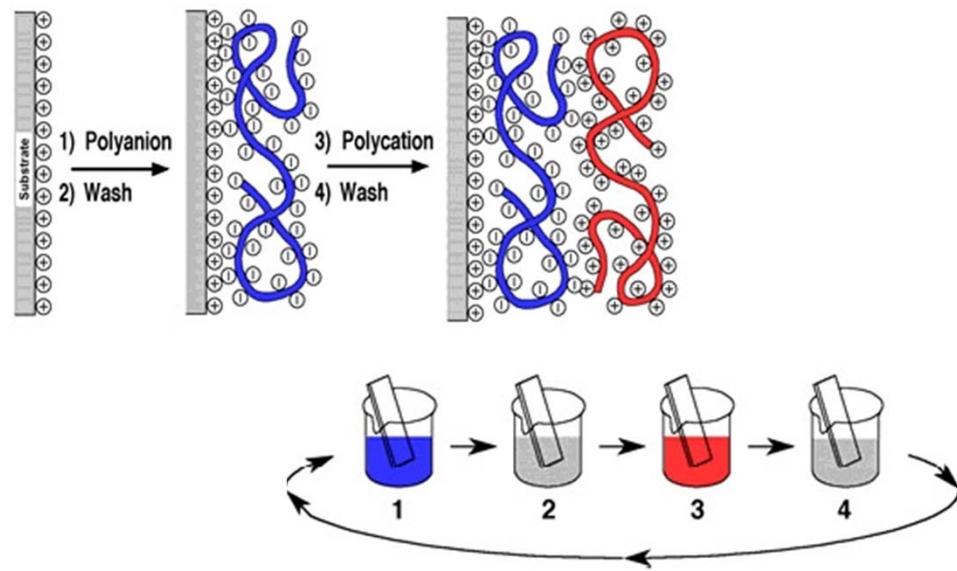
Edmiston et al. J. Am. Coll. Sur. (2006) 203(4): 481-489  
Leaper et al. Int. Wound J. (2011) 8: 556-566

Courtesy of S. Rothenburger

Degradable  
Non-degradable  
(Antibiotic eluting  
bone cement)

# Self-Assembled Antimicrobial-Containing Coatings

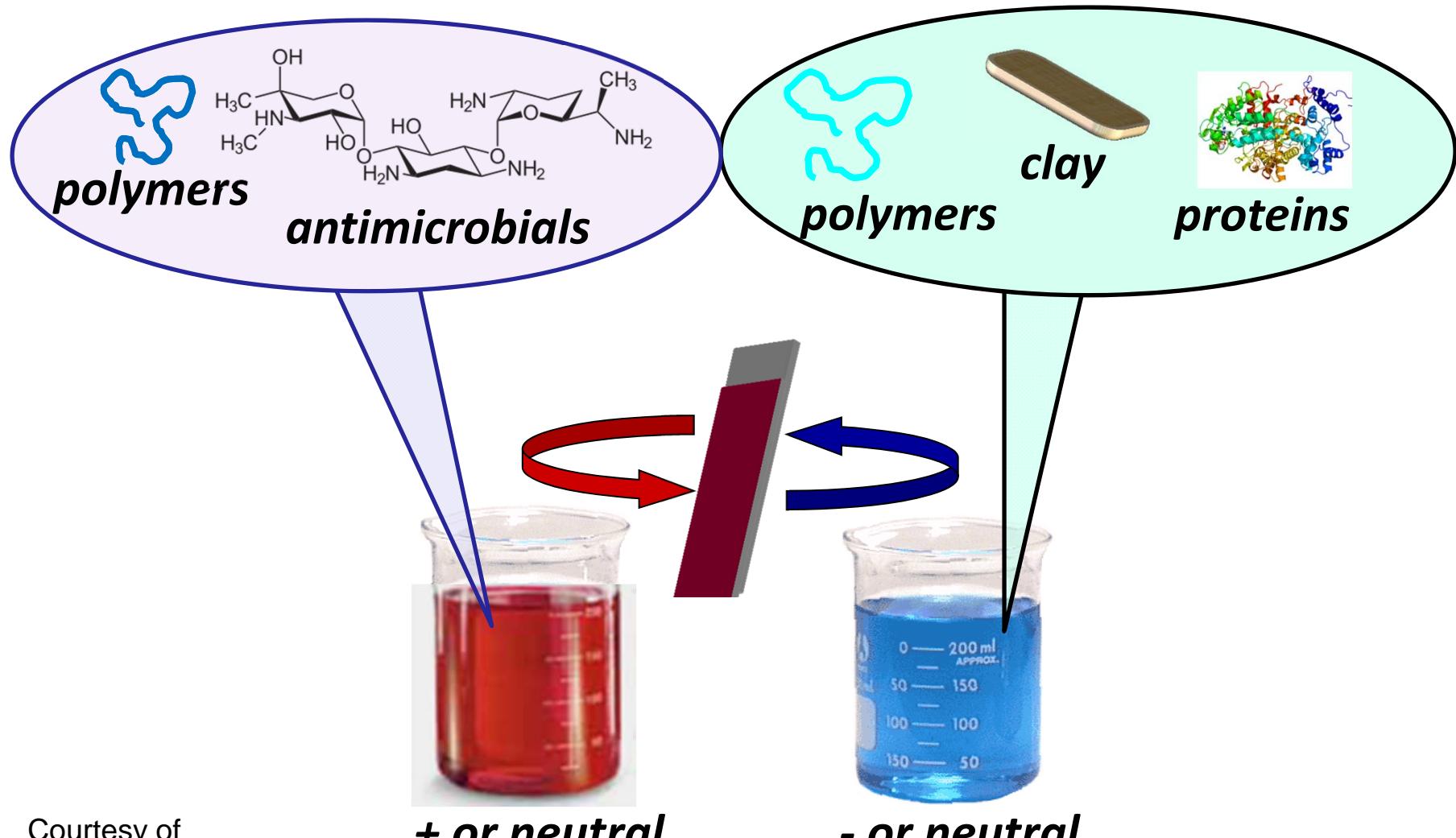
## Layer-by-Layer (LbL) thin-film self assembly



G. Decher  
Science 277: 1232-1237 (1997)

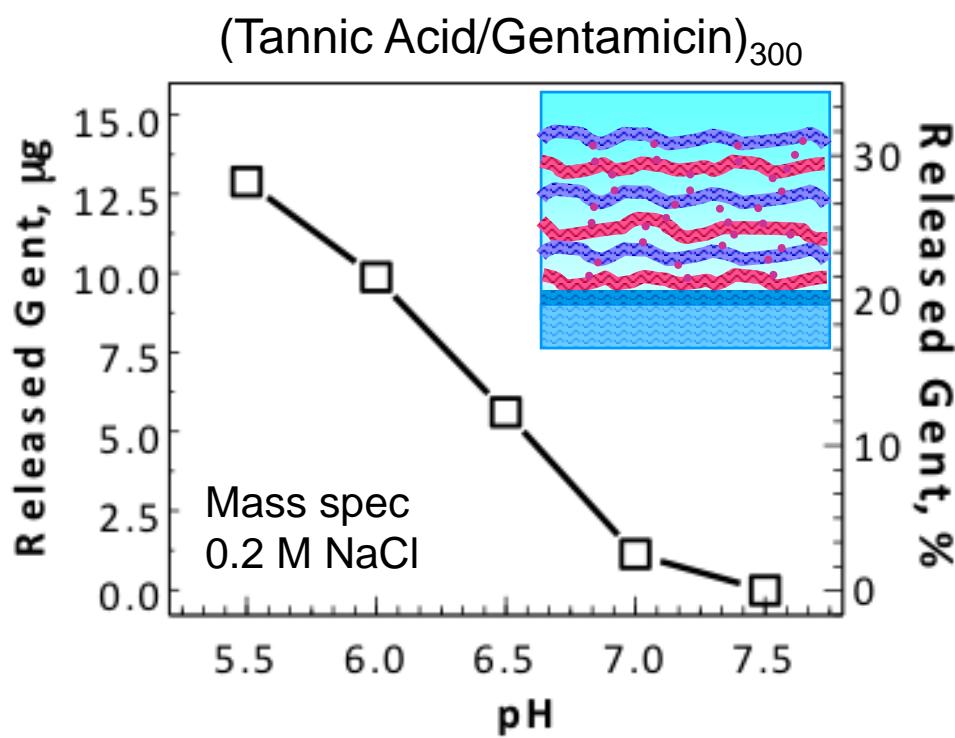
Non line-of-sight rapid  
deposition technology

# Multilayer Components



Courtesy of  
S. Sukhishvili  
Stevens Institute of Tech.

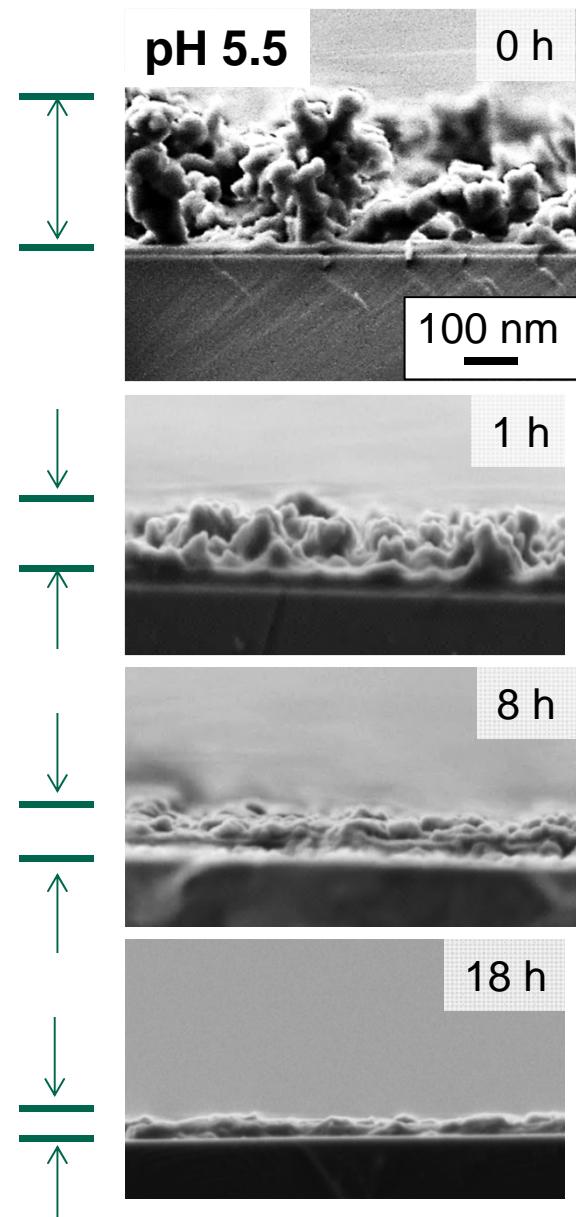
# pH-Triggered Self-Defensive Coatings



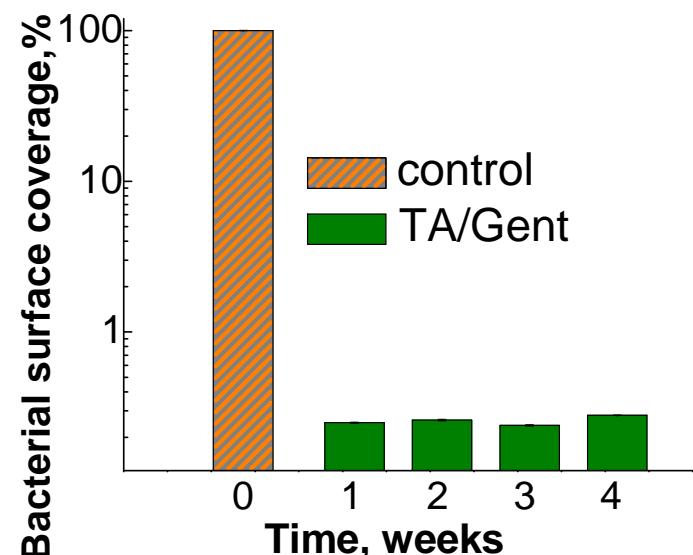
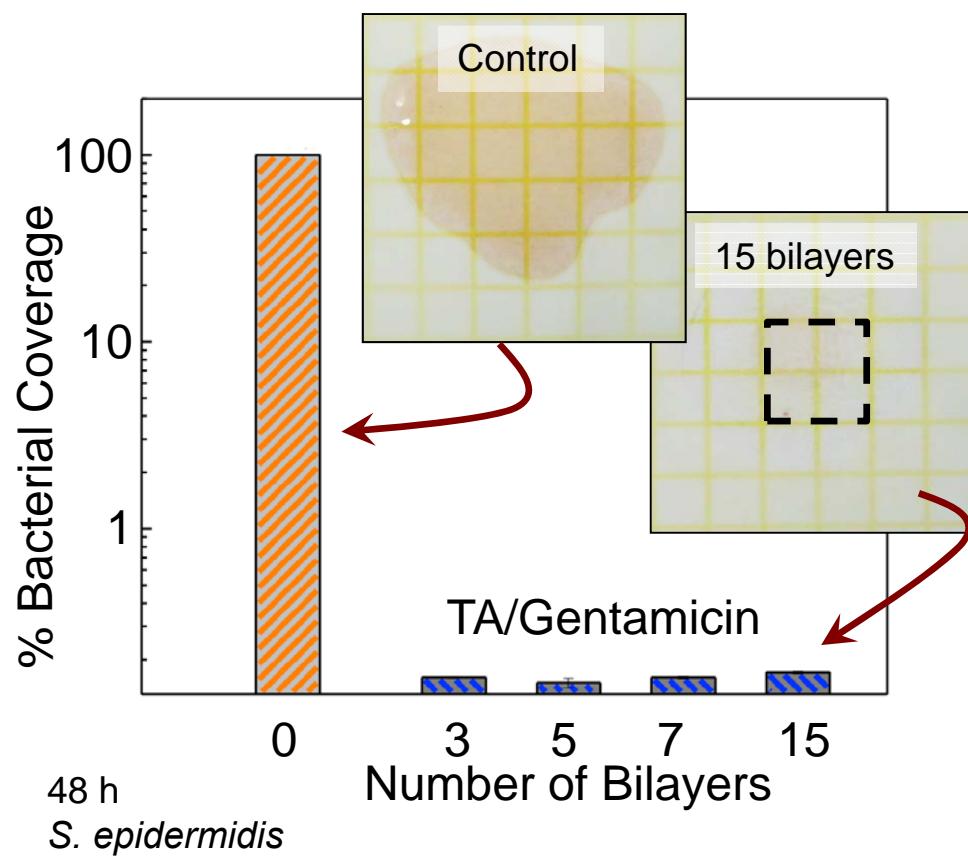
Sukhishvili et al.

ACS Nano, submitted (2014)

Biomacromolecules 11(12) 3448-56 (2011)

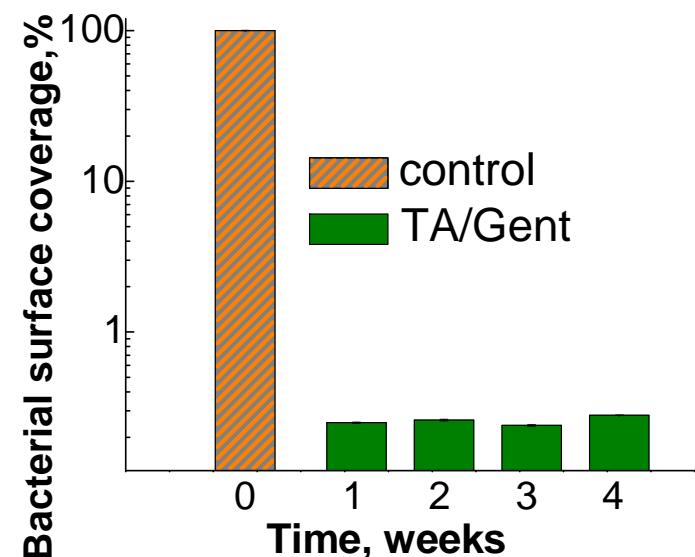
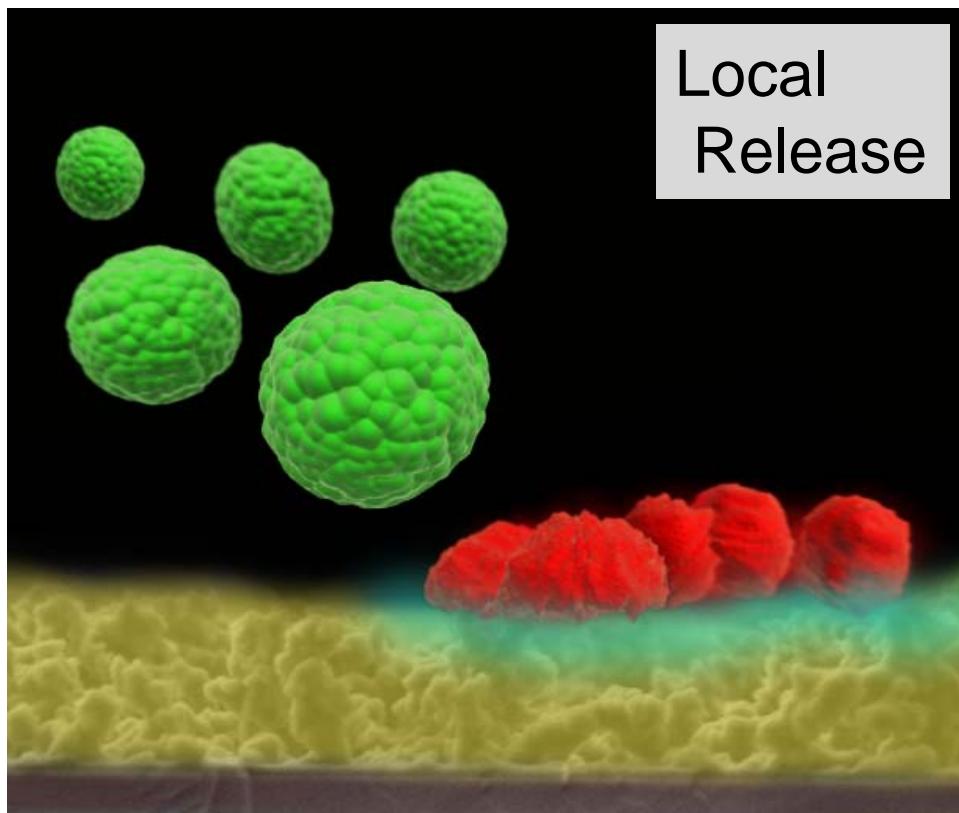


# pH-Triggered Self-Defensive Coatings



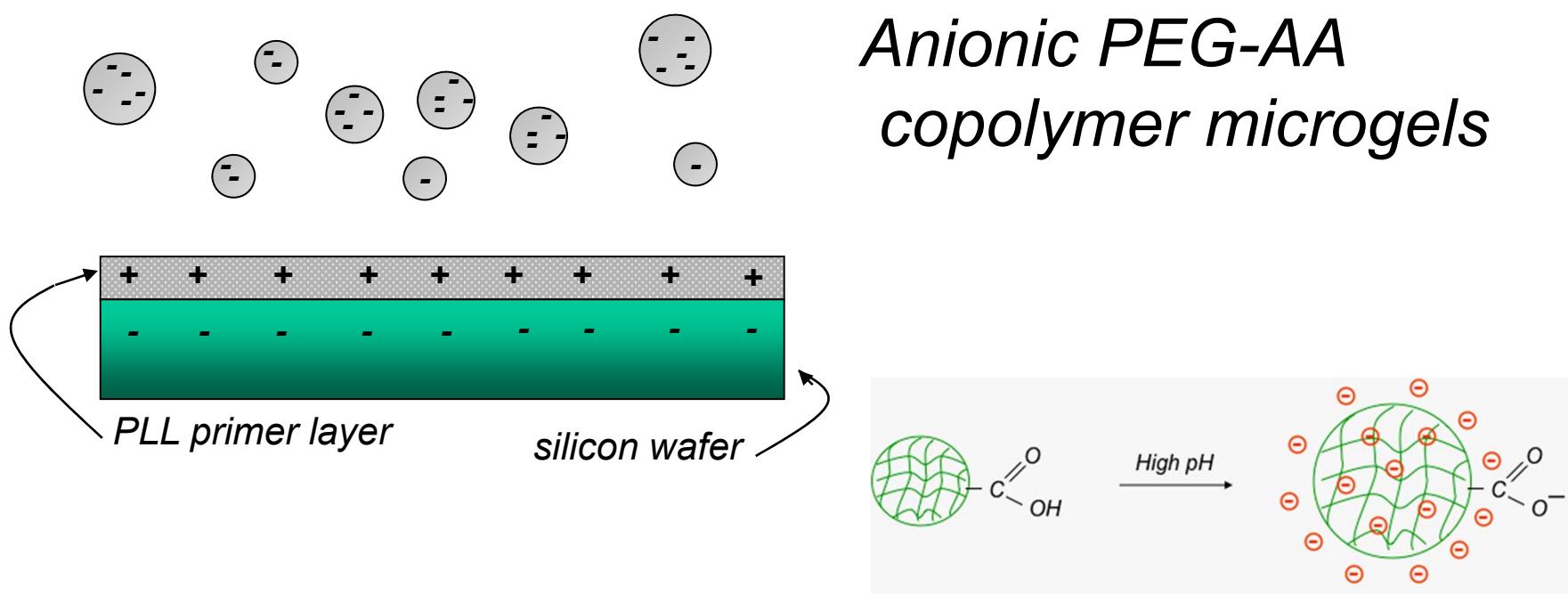
*Sukhishvili et al.*  
ACS Nano, submitted (2014)  
Biomacromolecules 11(12) 3448-56 (2011)

# pH-Triggered Self-Defensive Coatings



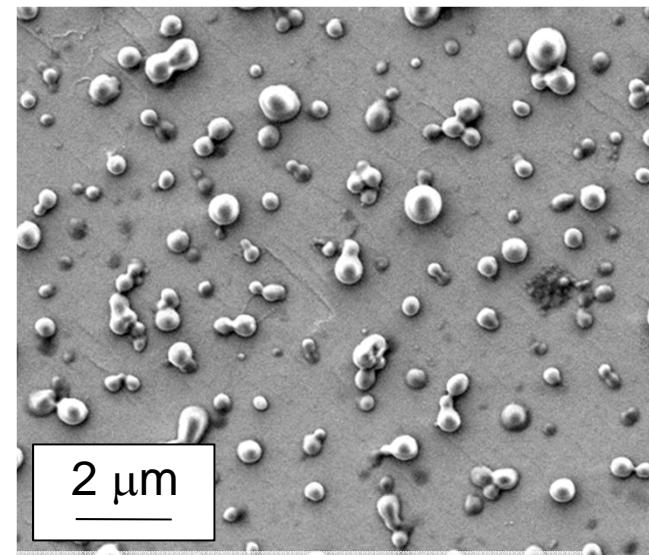
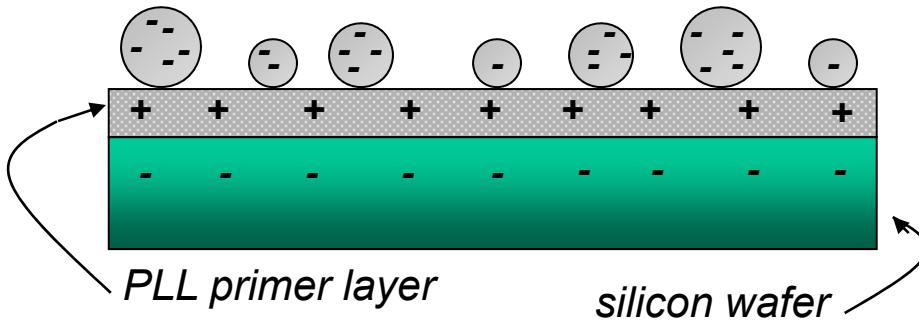
*Sukhishvili et al.*  
ACS Nano, submitted (2014)  
Biomacromolecules 11(12) 3448-56 (2011)

# Hierarchical Microgel Self-Assembly to Create Infection-Resisting Multifunctional Surfaces



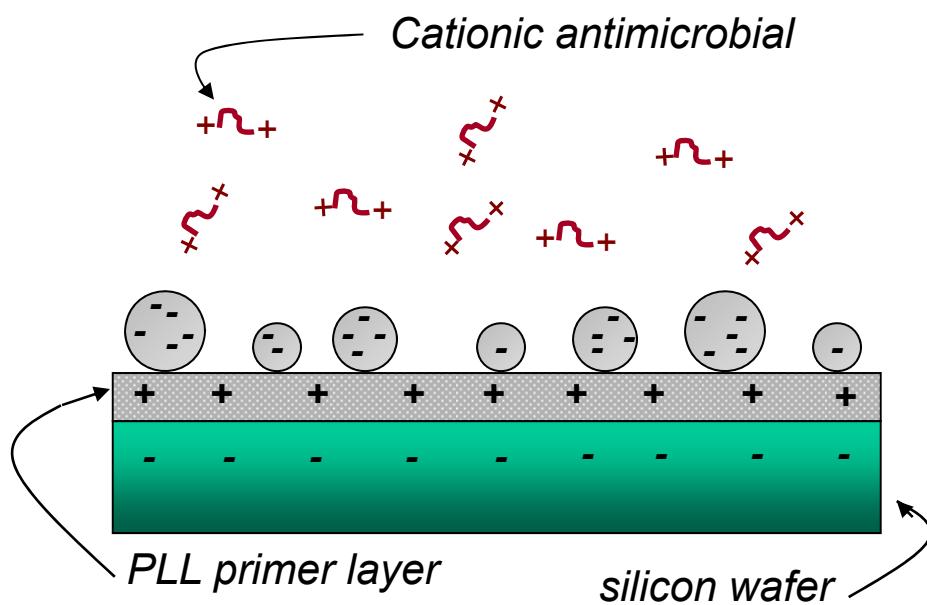
# Hierarchical Microgel Self-Assembly to Create Infection-Resisting Multifunctional Surfaces

*Laterally modulated  
cell adhesiveness*



Q. Wang et al,  
*Appl. Matls. & Interfaces*  
V4, 2498-2506 (2012)

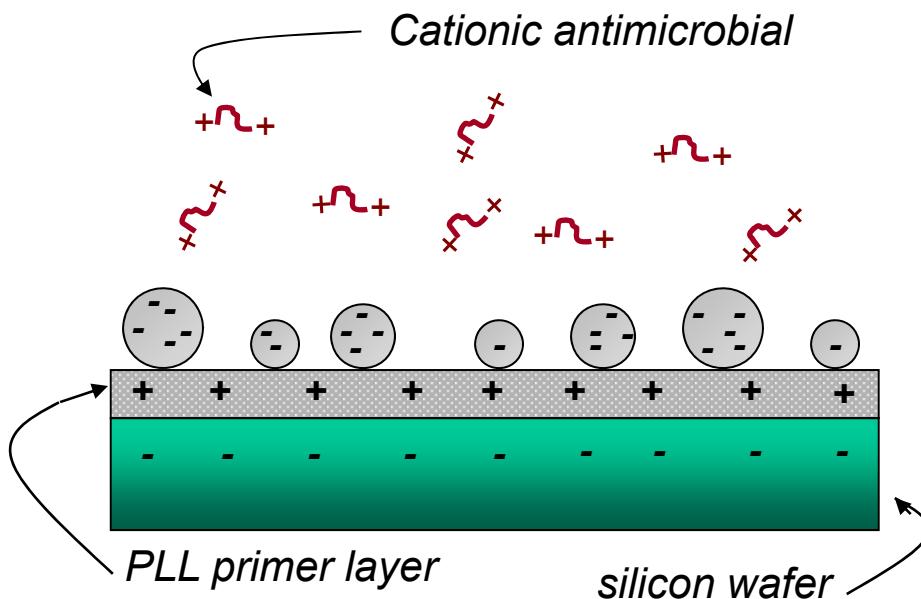
# Hierarchical Microgel Self-Assembly to Create Infection-Resisting Multifunctional Surfaces



Some cationic antimicrobials:

- vancomycin
- gentamicin
- tobramycin
- amikacin
- antimicrobial peptides/peptoids
- etc..

# Hierarchical Microgel Self-Assembly to Create Infection-Resisting Multifunctional Surfaces



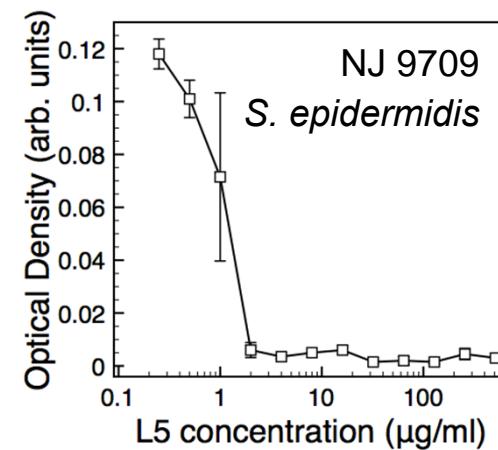
## L5 antimicrobial peptide

PAWRKAFRWAWRMLKKAA

Lactoferrin derived

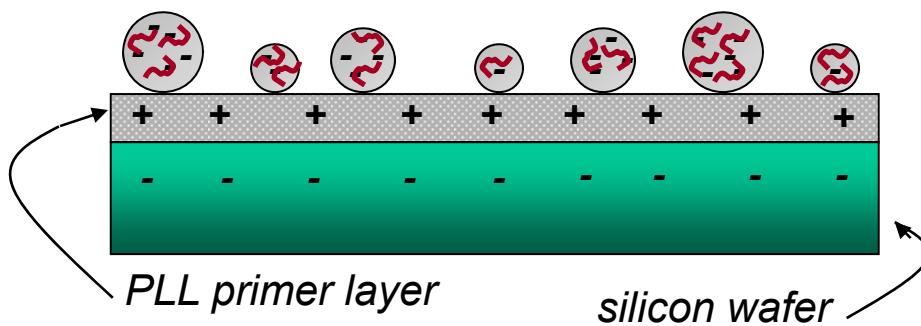
$M_w = 2274$  Da

6 positive charges at pH 7.4

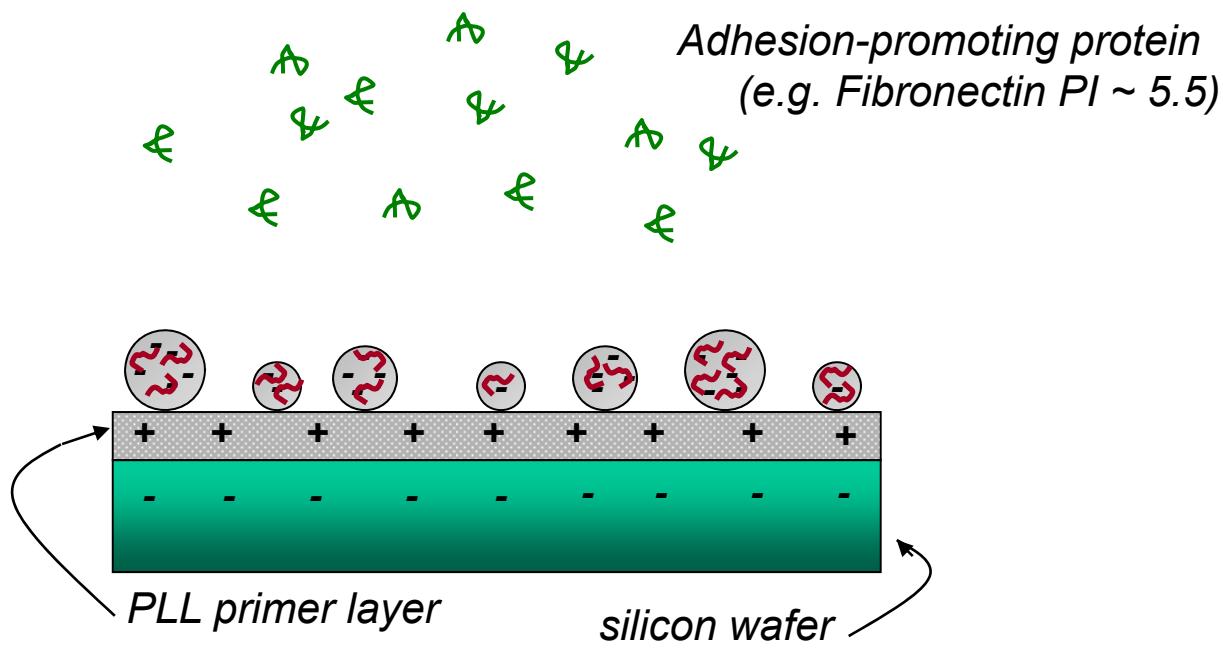


# Hierarchical Microgel Self-Assembly to Create Infection-Resisting Multifunctional Surfaces

*Antimicrobial-loaded  
microgels*

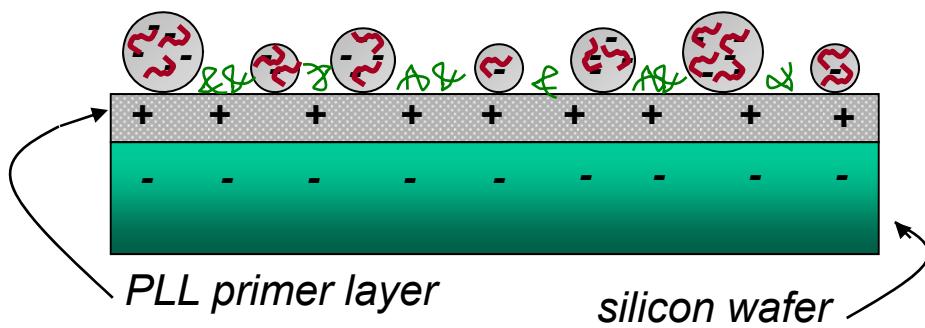


# Hierarchical Microgel Self-Assembly to Create Infection-Resisting Multifunctional Surfaces



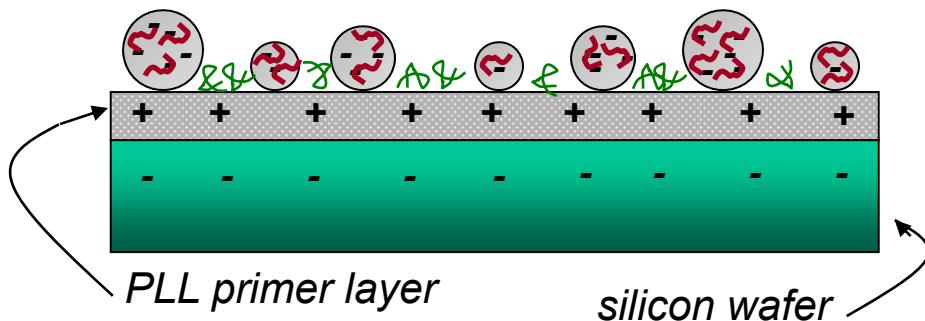
Q. Wang et al,  
Appl. Matls. & Interfaces  
V4, 2498-2506 (2012)

# Hierarchical Microgel Self-Assembly to Create Infection-Resisting Multifunctional Surfaces



Q. Wang et al,  
Appl. Matls. & Interfaces  
V4, 2498-2506 (2012)

# Hierarchical Microgel Self-Assembly to Create Infection-Resisting Multifunctional Surfaces



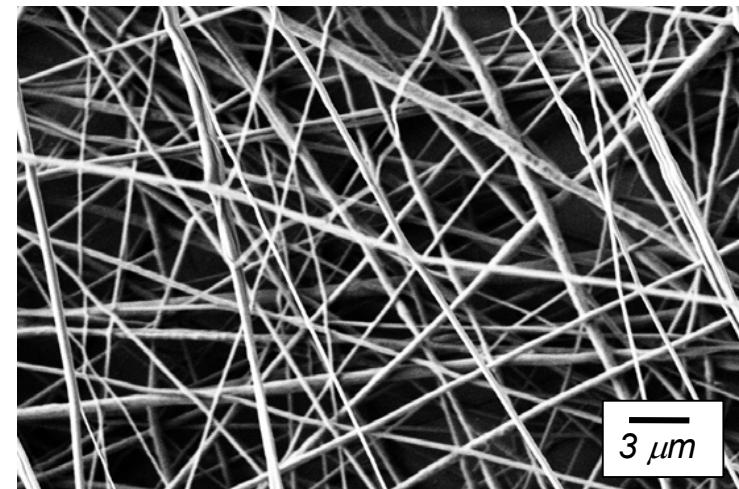
- > Non line-of-sight deposition
- > Laterally modulated cell adhesiveness
- > Post-deposition antimicrobial loading
- > Self-defensive antimicrobial release

# Biomaterials-Associated Infection of Tissue-Engineering Scaffolds

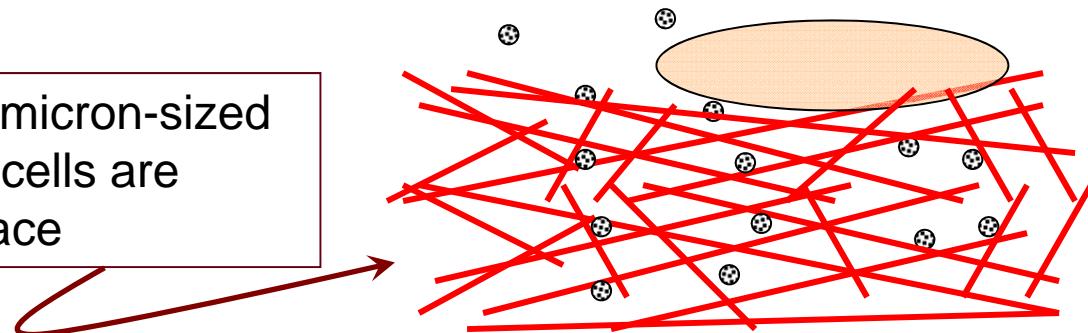
Kuijper, Grainger, Busscher et al.,  
*Assessing infection risk in implanted  
tissue-engineered devices*,  
Biomaterials, 28 (34): (2007) 5148-5154.

Nair, Kretlow, Mikos, and Kasper,  
*Infection and tissue engineering in  
segmental bone defects - a mini review*,  
Current Opinion in Biotech. 22 (2011) 721.

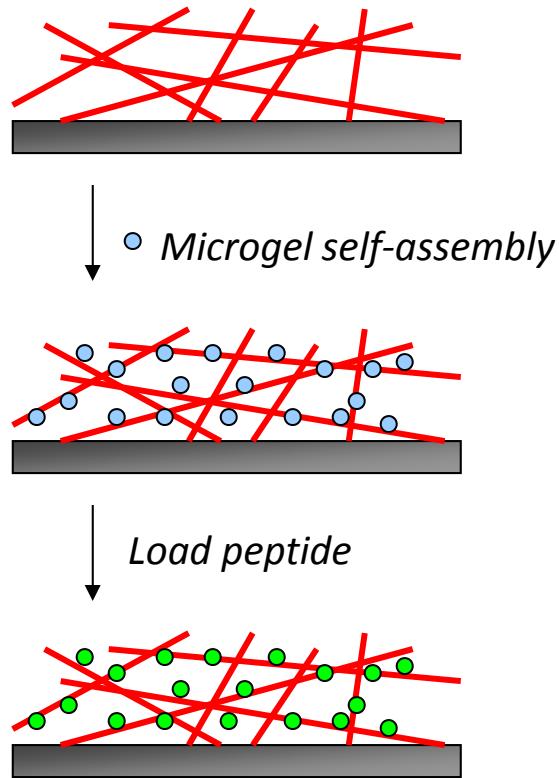
*Electrospun nanofiber mat*



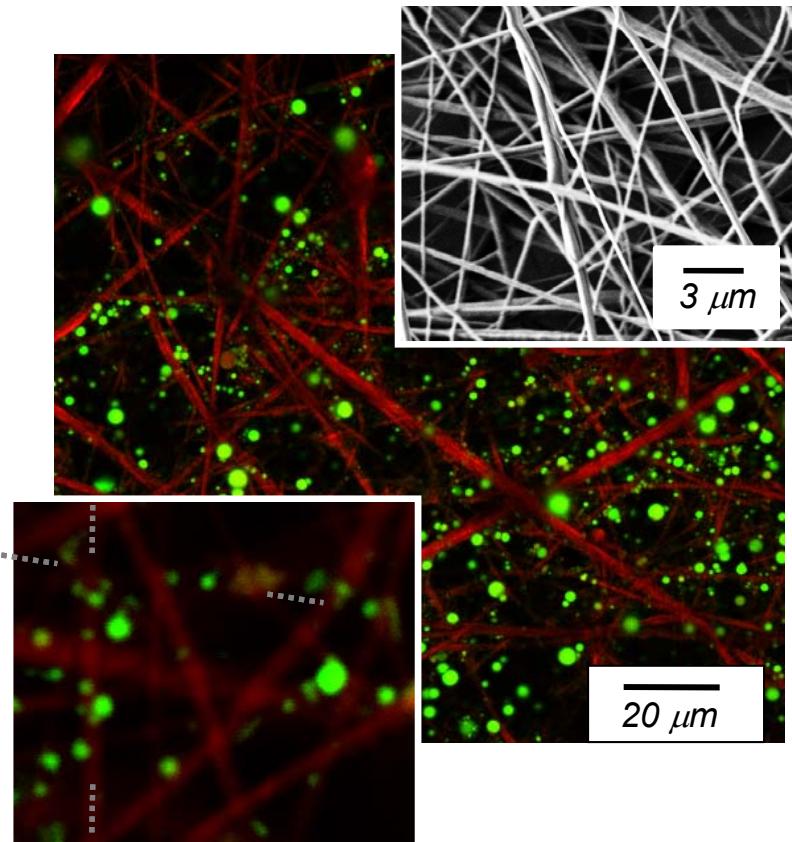
Bacteria can infiltrate ~micron-sized  
interstices while tissue cells are  
constrained to the surface



# Microgel Self-Assembly within Nanofiber Mats

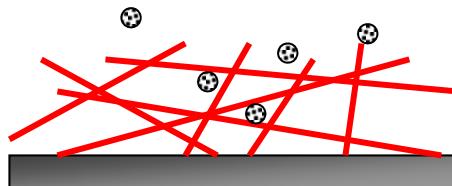


PCL-Chitosan nanofibers

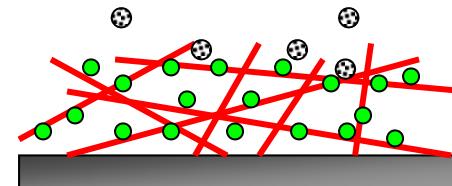


Texas Red conjugates to amines on Chitosan.  
FITC-terminated L5 peptide

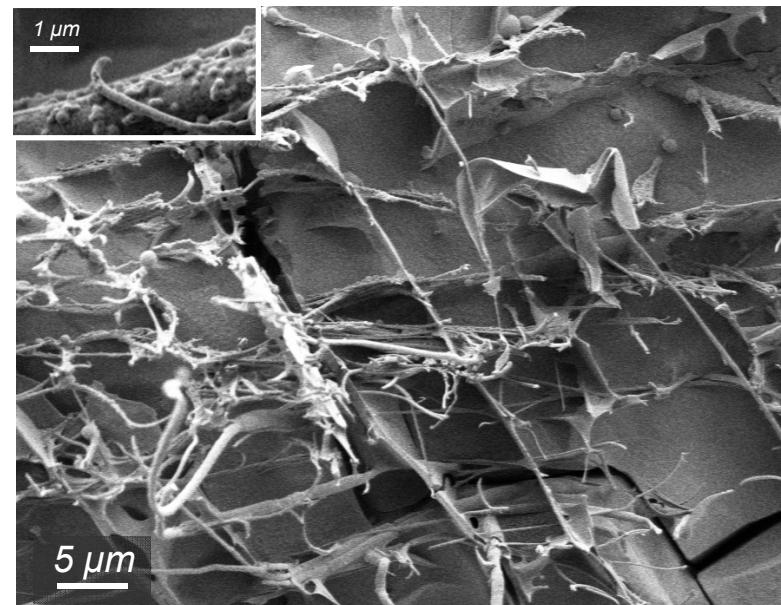
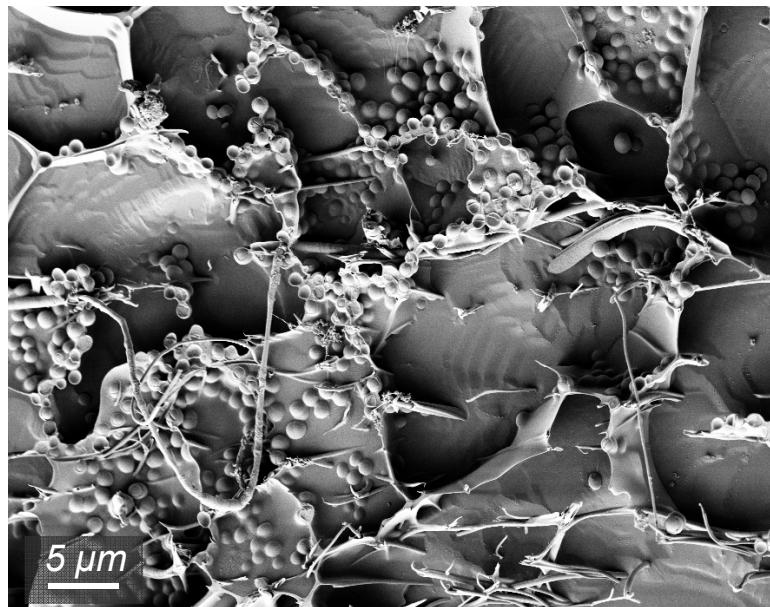
# Peptide-Loaded Microgel-Modified Nanofibers Resist *S. aureus* Colonization



unmodified scaffold



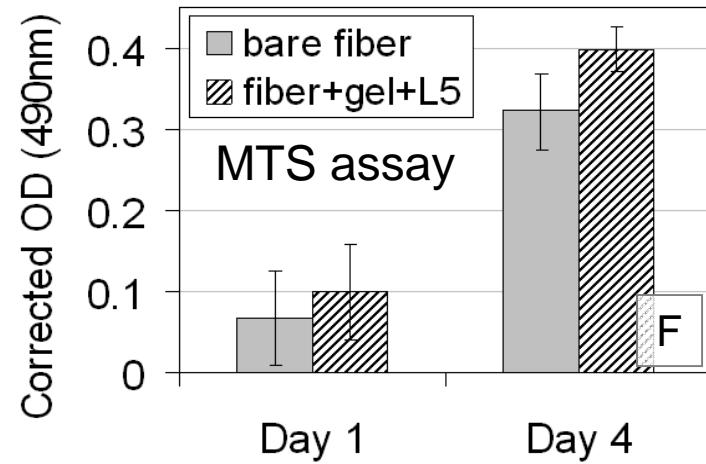
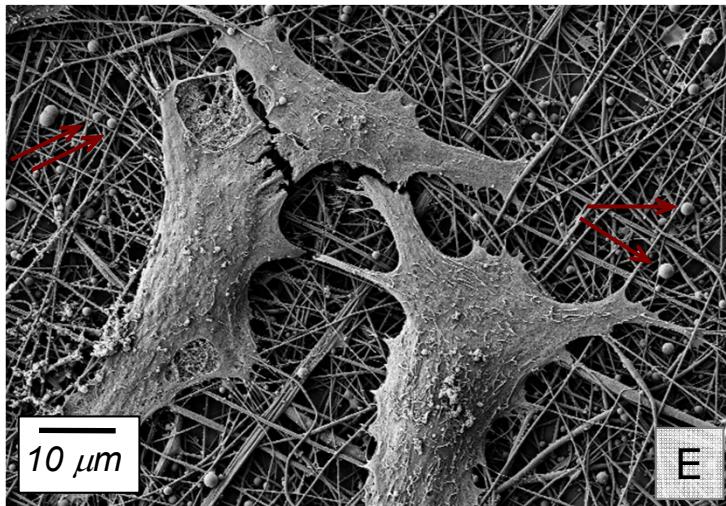
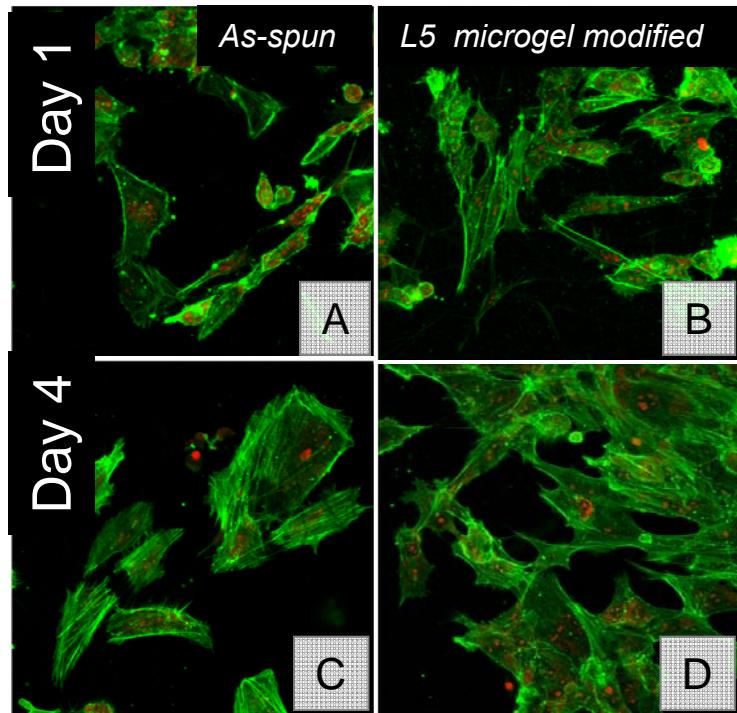
Microgel/peptide-modified scaffold



Cryo-SEM of fractured hydrated fiber mat

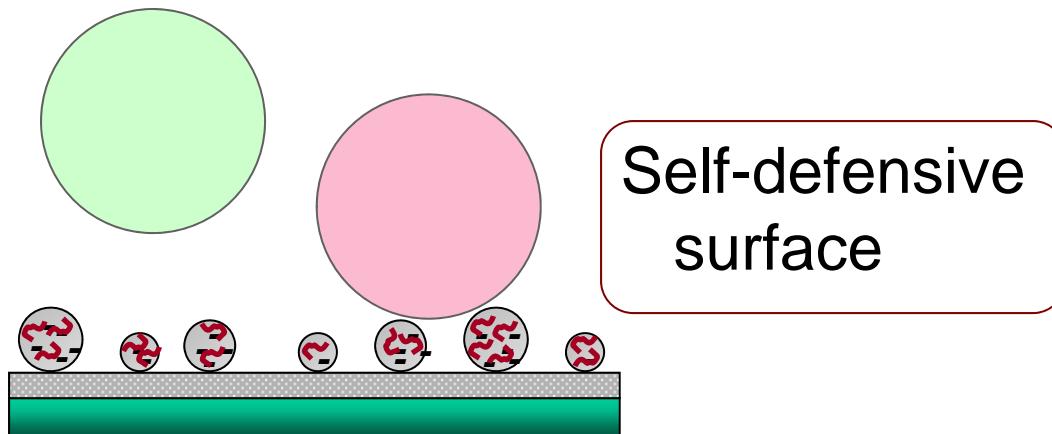
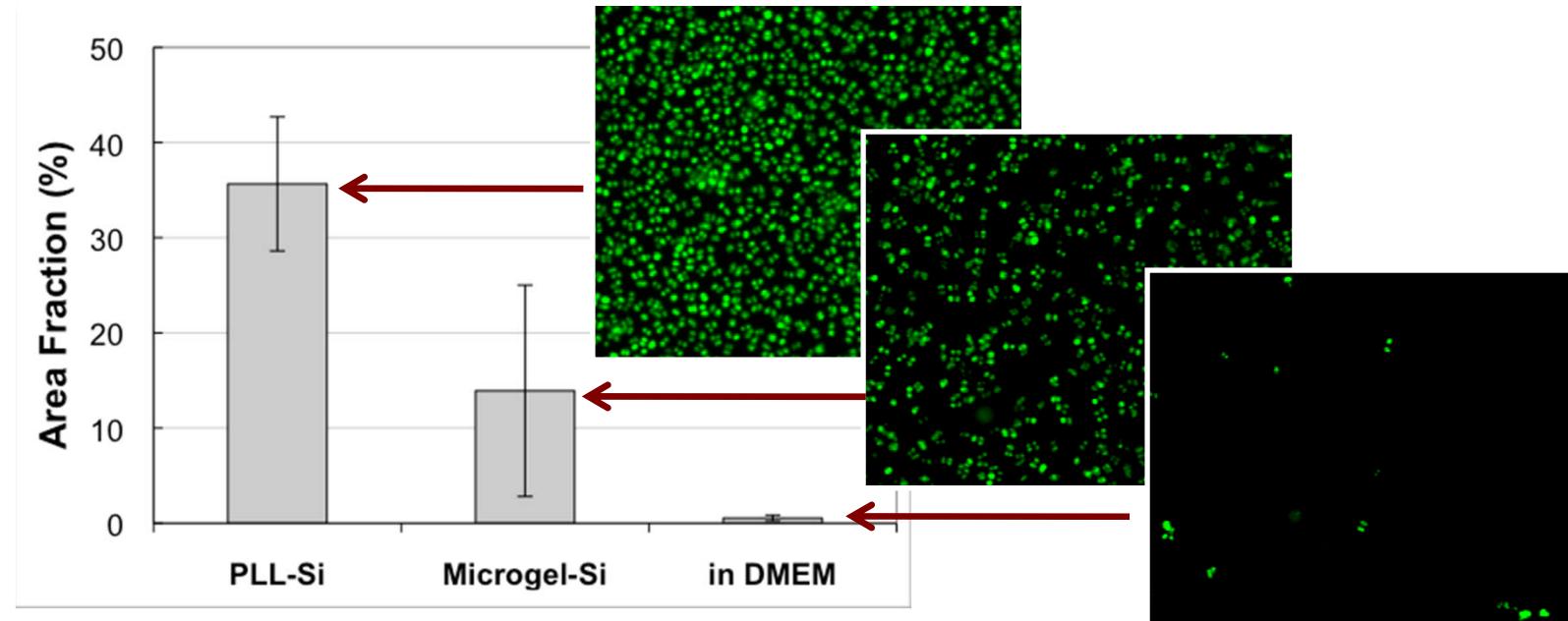
Q. Wang et al,  
*Adv. Healthcare Mats.*  
(2013)

# Osteoblast Response to Microgel-Modified Nanofiber Mats



Q. Wang et al,  
Adv. Healthcare Mats.  
(2013)

# Triggered Antimicrobial Release



Self-defensive  
surface

*L5-loaded microgel-modified PCL-chitosan nanofibers after soaking in DMEM for 4 days at 37 °C then inoculated w/ S. aureus and cultured in TSB for 8 h.*

# A Next-Generation Paradigm for Biomaterials Science and Engineering

The current generation of biomaterials has to a great extent been defined by a major paradigm shift from the pre-1990's perspective of creating biologically inert synthetic surfaces to the current perspective of creating surfaces that controllably interact with host tissue.

From this shift, a new international community emerged that marries skills from cell and molecular biology with those from physical sciences and engineering to an extent almost unthinkable twenty years ago.

The biomaterials community now needs a similar paradigm shift so it can not only regulate tissue-cell/material interactions but do so while simultaneously controlling bacterial-cell/material interactions.



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[http://www.stevens.edu/  
ses/biomaterials/conference](http://www.stevens.edu/ses/biomaterials/conference)

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